



IMPROVING HEALTH FOR BETTER FUTURE LIFE: STRENGTHENING FROM BASIC SCIENCE TO CLINICAL RESEARCH

Edited by
Muthmainah, Hanik Badriyah Hidayati and Budi Yanti

IMPROVING HEALTH FOR BETTER FUTURE LIFE: STRENGTHENING FROM BASIC SCIENCE TO CLINICAL RESEARCH

The proceedings of the 3rd International Conference on Health, Technology, and Life Science (ICO-HELICS 2022) shared ideas, pre-clinical and clinical research results, and literature review, on various aspects of medical science including heart disease, stroke, cancers, vaccines, infections, immunological disease, reproductive health, pharmacology and other health diseases. The proceedings aim to deliver new insights to the knowledge and practice of health workers and equip them in providing the best quality health care and clinical outcomes.

As the idea of advanced clinical research originated from basic or fundamental research, it explores the life processes that are universal in their application to scientific knowledge. Therefore, these proceedings will also be of interest to academics, practitioners, health workers, and professionals involved in medical research.



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PROCEEDINGS OF THE 3RD INTERNATIONAL CONFERENCE ON HEALTH, TECHNOLOGY
AND LIFE SCIENCES (ICO-HELICS III), SURAKARTA, INDONESIA, 19–20 NOVEMBER 2022

Improving Health for Better Future Life: Strengthening from Basic Science to Clinical Research

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CRC Press

Taylor & Francis Group

Boca Raton London New York Leiden

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business

A BALKEMA BOOK

First published 2023
by CRC Press/Balkema
4 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN

and by CRC Press/Balkema
2385 NW Executive Center Drive, Suite 320, Boca Raton FL 33431

CRC Press/Balkema is an imprint of the Taylor & Francis Group, an informa business

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British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Library of Congress Cataloging-in-Publication Data
A catalog record has been requested for this book

ISBN: 978-1-032-68635-6 (hbk)

ISBN: 978-1-032-69337-8 (pbk)

ISBN: 978-1-032-69340-8 (ebk)

DOI: 10.1201/9781032693408

Typeset in Times New Roman
by MPS Limited, Chennai, India

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Preface

Many areas in health and medical research have been consistently successful in providing the best quality health care and best clinical outcomes. Astonishing enhancement of heart disease, stroke, cancers, vaccines, infections, immunological disease, and other health diseases is evidence of the power of science to save and improve lives. Medical researchers who work in clinical research have studied health and illness in people, which also proves and protects public health. Furthermore, the idea of advanced clinical research originated from basic research or fundamental research, the study of life processes that are universal in their application to scientific knowledge. Clinical Research addresses important questions of normal function and disease using human subjects. The researchers need to expand their capabilities by adding up the medical updates through journals, scientific discussions, and conferences.

To strengthen the clinical research, a scientific conference need to add to the annual agenda. Therefore, the Medical Faculty of Universitas Sebelas Maret Indonesia which is among the top medical faculty in Indonesia would like to present the **Third International Conference on Health, Technology, and Life Science (ICO-HELICS)**.

ICO-HELIC 2022 is held fully online and enhance with virtual reality experience to provide all participants with interactive learning experiences in this International Conference on Health, Technology, and Life Science.

Dr. Revi Gama Hatta Novika, SST.,M.Kes



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Acknowledgements

Prof. Chien-Sheng Chen (*Department of Food Safety, National Cheng Kung University*)

Prof. Irawan Satriotomo, PhD (*Senior Researcher in Neurodegenerative Disease,
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Dr. Yugeesh Lankadeva, PhD (*Head of Translational Cardiovascular and Renal
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*Medical (basic science, clinical, translational research,
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A cost-effectiveness analysis of ferric carboxymaltose in patients with heart failure and iron deficiency: A systematic review

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ABSTRACT: Iron deficiency is one of the heart failure comorbidities. This study aims to evaluate and conclude the cost-effectiveness of ferric carboxymaltose in heart failure patients with iron deficiency. This was a systematic review of all articles collected from PubMed, Scopus, Web of Science, EBSCO, ProQuest, Science Direct, and Global Health Databases, published from 2012 to 2022. Seven studies from 679 articles were included. One article used the Markov model study design, five articles used a model-based study, and one article used a cost-utility approach. South Korea has the highest ICERs at \$18.254/QALY. Ferric carboxymaltose is cost-effective for heart failure with iron deficiency, with an average ICER value of \$7,814/QALY and a median value of \$6,678/QALY.

1 INTRODUCTION

Heart failure still a major health problem with a global prevalence of 64.3 million patients (Roger 2021). These can cause higher re-hospitalization, hospitalization duration, and economic burden (Virani *et al.* 2020). A high rate of heart failure cases led to high estimated medical costs, with an expense of 31 billion USD in 2012 and predicted to increase the cost by about 127% in 2030 (Mozaffarian *et al.* 2016).

European Society of Cardiology admits iron deficiency as a heart failure comorbidity relates to reducing activity capacity, increasing hospitalization risks, worsening the Health-Related Quality of Life (HRQoL), and death (Martens *et al.* 2018; McMurray *et al.* 2012). Those have been reported at 50% in chronic heart failure and 80% in acute heart failure patients (Cohen-Solal *et al.* 2014). Until 2021, some studies have proved the efficacy and safety of ferric carboxymaltose intravenous, which can improve the clinical condition, increase HRQoL, decrease hospitalization rate, and reduce the duration of hospitalization (McEwan *et al.* 2021; van Veldhuisen *et al.* 2017).

According to the condition above, several studies raised from clinical studies to economic studies, such as cost-effectiveness analysis (CEA), to support the stakeholders in each country to evaluate the economic impact and the effectiveness of ferric carboxymaltose in patients with heart failure and iron deficiency (Hofmarcher & Borg 2015; van Veldhuisen *et al.* 2017). Those studies report varied results and need to be systematically reviewed about studies' evidence related to ferric carboxymaltose cost-effectiveness and bring a systematic scientific conclusion (Page *et al.* 2021).

2 METHODS

2.1 Study design

This was a systematic review using the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) protocol (Page *et al.* 2021).

2.2 Searching strategy

We obtained the articles using an electronic database, namely PubMed (MEDLINE), Scopus, Publons, Science Direct, EBSCO, ProQuest, and Global Health databases. We used varied keywords, including “cost-effectiveness”, “ferric carboxymaltose”, “heart failure”, and “iron deficiency” and continued with the Boolean operation strategy.

We applied articles from 2012 to 2022 because FCM was a relatively new therapy regimen for heart failure. The first efficacy of FCM in heart failure was the 2007 FAIR-HF (Anker *et al.* 2009). It grew until 2012 in ESC guidelines for heart failure patients with iron deficiency (McMurray *et al.* 2012). Ultimately, cost-effectiveness research of the FCM began to emerge in the last ten years worldwide.

2.3 Article criteria

The article inclusion criteria used were (i) relevant economic evaluation studies, (ii) patients aged >18 years old who were diagnosed with symptomatic heart failure HFrEF or NYHA class II-IV with iron deficiency, (iii) included ICER and QALY outcomes, (iv) English journal, (v) published from 2012–2022, (vi) evaluated ferric carboxymaltose cost-effectiveness, (vii) using ferric carboxymaltose as therapy, (viii) full-text accessed.

Articles would be excluded if (i) review article or protocol or an abstract, (ii) the population was heart failure patients without iron deficiency or heart failure patients with iron deficiency but received iron supplementation except for ferric carboxymaltose, (iii) patients with comorbidities such as chronic kidney disease and cancer.

2.4 Study selection

The results from article searching would be inserted into the Mendeley desktop with each database folder; then the summary would be put into Microsoft Excel. Afterward, these results would be screened by QFS and NPI independently according to the title and abstract. We would discuss if there were different results and would be deliberated with the RPF if the discussion ended without a deal.

2.5 Extraction and data synthesis

All extractions were made by QFS and NPI independently according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) Quality Assessment 2013 (Kemmak *et al.* 2021). The mark ‘Y’ got a score of 1, ‘P’ scored 0.5, and ‘N’ scored 0. All results were classified into high quality (>85%), excellent quality (<70–85%), good quality (<55–70%), and low quality (<55%). All variations of extraction results and critical appraisal were discussed with RPF and YAM. The evaluated articles were extracted in the results table. Data synthesis was conducted using a narrative descriptive method because the study results varied among countries (Franklin & Thorn 2019; Rashki Kemmak *et al.* 2022).

3 RESULTS

We found 679 articles. After we excluded 204 duplicated articles, 178 review articles, abstracts, or protocols, 207 articles that did not relate to ferric carboxymaltose, 63 articles that did not include iron deficiency, and 20 articles that did not meet the inclusion and exclusion criteria, we ended up with 7 full-text eligible articles (Figure 1).

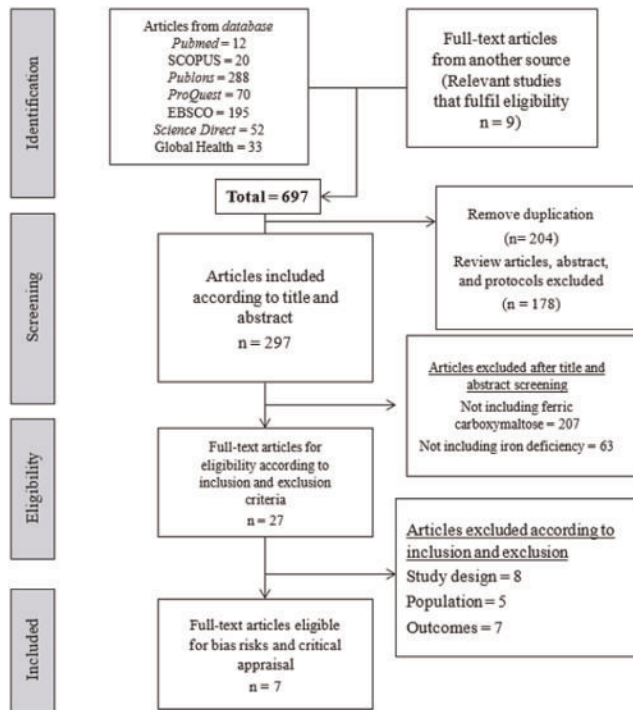


Figure 1. Flowchart of systematic review according to PRISMA.

Table 1 explains the summary of seven selected studies in this systematic review. The patients were HFrEF with iron deficiency. Ferric carboxymaltose as the choice of therapy was the primary intervention in this article. The main output to be valued was ICER and QALY. Meanwhile, Table 2 was the summary of critical appraisal using the CHEERS Checklist 2013.

Table 1. The summary of selected studies.

Author, year	Currency/ year	Threshold	Health Outcomes (QALY)	Incremental QALY*	Incremental Costs	ICER
(Comín-Colet <i>et al.</i> 2015)	€/2013	€30.000	0.335	0.037	€824,17/€597,59	€6,123/ QALY
(Gutzwiller <i>et al.</i> 2012)	€ and £ / spain 2009	€22.200– €33.300 (£20.000– 30.000)	0.336	0.038	€852(£768)/€687 (£619)	€4,414 (£3,977)/ QALY
(Hofmarcher & Borg 2015)	SEK and €/2014	SEK 500.000 (€54.300)	0.036	0.038	SEK 8,602 (€935)/ SEK 8,512 (€632)	SEK 75,389 (€8,194)/ QALY
(Hofmarcher <i>et al.</i> 2018)	€/2017	€45.000	N/A	0.050	Denmark (€1,082) Finlandia (€961) Norwegian (€1,275) Sweden (€1,068)	€6,500– €9,000/ QALY
(Lim <i>et al.</i> 2014)	\$/2012	N/A	N/A	0.021	Incremental cost \$466	\$22,192 (₩25,01 0.451)/ QALY

(continued)

Table 1. Continued

Author, year	Currency/ year	Threshold	Health Outcomes (QALY)	Incremental QALY*	Incremental Costs	ICER
(Rognoni & Gerzeli 2019)	€/2018	€20.000	0.703	0.061	€3,296/€3,699	€4,414/ QALY
(McEwan <i>et al.</i> 2021)	GBP (£), USD (\$), EUR (€), CHF (Fr.) /2020	UK: £20.000; USA: \$100.000; Switzerland: Fr.50.000; Italy: €30.000	UK 0.430; Italy 0.430; Switzerland 0.440; USA 0.440	N/A	UK £10,700/£10,839 Italia €26,489/ €25,939 Swiss Fr45,028/Fr47,733 USA \$67,475/ \$70,896	UK domi- nant, Italia €1.269/ QALY, Swiss dominant, USA dominant

*QALY, *Quality Adjusted Life Years*; FCM, *Ferric Carboxymaltose*; ICER, *Incremental Cost Effectiveness Ratio*; ESC, *European Society of Cardiology*; SEK, *Sweden Krona*; UK, *United Kingdom*; USA, *United States of America*; USD, *United States Dollar*; EUR, *Euro*; CHF, *Switzerland Franc*; GBP, *British pound sterling*; N/A, *Not Applicable*; €, *Euro*; £, *Pound*; \$, *Dollar*; Fr., *Franc*.

Table 2. Analysis results of bias risks using CHEERS 2013.

Item no	Checklist	Comin- Colet <i>et al.</i>	Gutz- willer <i>et al.</i>	Hofmar- cher and Borg	Hof- marcher <i>et al.</i>	Lim <i>et al.</i>	Rognoni and Gerzeli	McEwan <i>et al.</i>
1	Title	Y*	P*	Y	P	Y	Y	Y
2	Abstract	P	P	P	P	Y	P	Y
3	Background and objec- tives	Y	Y	Y	Y	Y	Y	Y
4	Target population and subgroups	P	P	P	P	Y	P	Y
5	Setting and location	P	Y	Y	Y	P	Y	Y
6	Study perspective	Y	Y	Y	P	Y	Y	Y
7	Comparators	Y	Y	Y	Y	Y	P	Y
8	<i>Time horizon</i>	Y	Y	Y	Y	Y	Y	Y
9	<i>Discount rate</i>	Y	Y	Y	Y	N*	Y	Y
10	Choice of health outcomes	Y	Y	Y	Y	Y	Y	Y
11a	Measurement of Effec- tiveness (<i>single study- based</i>)	Y	Y	Y	Y	Y	N/A*	Y
11b	Measurement of effective- ness (<i>model-based</i>)	N/A	N/A	N/A	N/A	N/A	Y	N/A
12	Measurement and evalua- tion of preference based outcomes	N	Y	Y	Y	Y	Y	Y
13a	Estimating resources and costs (<i>single study-based</i>)	Y	Y	Y	Y	Y	N/A	Y
13b	Estimating resources and costs (<i>model-based</i>)	N/A	N/A	N/A	N/A	N/A	Y	N/A
14	Currency, price date, and conversion	P	Y	Y	Y	Y	P	Y

(continued)

Table 2. Continued

Item no	Checklist	Comin-Colet <i>et al.</i>	Gutzwiller <i>et al.</i>	Hofmarcher and Borg	Hofmarcher <i>et al.</i>	Lim <i>et al.</i>	Rognoni and Gerzeli	McEwan <i>et al.</i>
15	Choice of model	Y	Y	P	P	Y	Y	Y
16	Assumptions	Y	Y	Y	Y	Y	Y	N
17	Analytical methods	Y	Y	Y	Y	P	Y	Y
18	Study parameters	Y	Y	Y	Y	Y	Y	Y
19	Incremental costs and outcomes	Y	Y	Y	Y	Y	Y	Y
20a	Characterizing uncertainty (<i>single study-based</i>)	P	P	P	N	N	N/A	P
20b	Characterizing uncertainty (<i>model-based</i>)	N/A	N/A	N/A	N/A	N/A	Y	N/A
21	Characterizing heterogeneity	N	P	P	P	Y	N	Y
22	Study findings, limitations, generalizability, and current knowledge	Y	Y	Y	Y	Y	Y	Y
23	Source of funding	Y	Y	Y	Y	Y	Y	Y
24	Conflicts of interest	Y	Y	Y	Y	Y	Y	Y
	Quality of Article	Very Good	High	High	Very Good	High	High	High

*Y, Yes; N, No; P, Partially; N/A, Not Applicable

4 DISCUSSION

4.1 The threshold and ICER of every country in the selected study

This systematic review compared the cost-effectiveness by considering the economic threshold. Therefore, ICER was changed into USD/\$ (according to Purchasing Power Parity over Gross Domestic Product or GDP in 2022). The Rognoni dan Gerzeli' study from Italy showed a close difference between the threshold and ICER, with only \$17,001 (\$4,815/QALY for ICER and \$21,816 for the threshold) (Rognoni & Gerzeli 2019). Moreover, Hofmarcher dan Borg' study from Sweden had the highest difference between the threshold and ICER (\$8,938/QALY for ICER and \$59,230 for the threshold), which showed the possibility of using ferric carboxymaltose as therapy was highly cost-effective (Hofmarcher & Borg 2015).

4.2 The uncertainty analysis from selected studies

The results from seven studies showed a good situation equally to Deterministic Sensitivity Analysis (DSA), Univariate Sensitivity Analysis (USA), or Probabilistic Sensitivity Analysis (PSA), which were applied in economic evaluation. The average results in studies with PSA were in the upper right quadrant, which meant that the cost and effectiveness were higher. The differences in QALY, cost or ICER showed that FCM was cost-effective. Therefore, even though the cost was higher, FCM could increase the quality of life and apply to those countries.

4.3 The cost of ferric carboxymaltose therapy

The difference between Gross National Income (GNI) per capita and the health care system was not so obvious, whereas the GNI per capita in high-income countries (HIC), according

to the World Bank (2022), is >\$12,695. That's why the intervention cost and threshold of those countries were equally higher in FCM than in placebo.

FCM cost had various interpretations, with studies from North Europe countries, Norway, and Sweden, showing that FCM cost could cut the total treatment cost compared with a placebo. The FCM cost was the same high as the placebo in Denmark, but higher than the placebo in Finland (Hofmarcher *et al.* 2018). However, the effectiveness and the advantage to the patient's condition were higher with FCM therapy than with the placebo one, thus, we could say that FCM therapy was cost-effective.

On the other hand, the discount rate of FCM was not valid for six studies because of the short time horizon, which was 24–52 weeks. It's only the study by McEwan *et al.* that applied a discount rate with an amount of 3,5% for the UK and 3% for Switzerland, Italy, and the USA (McEwan *et al.* 2021). The age of the population used in seven studies (>60 years old, who were not productive in the majority) showed that the indirect medical cost of FCM therapy did not significantly affect the study results of FCM cost-effectiveness.

4.4 *The clinical outcomes of ferric carboxymaltose in QALY*

The average incremental QALY of FCM compared with the placebo was 0.041 QALY, which showed an increase in the patient's quality of life toward complete health. The highest clinical outcome was the study in Italy which showed a value of QALY 0.703 for FCM, with an incremental QALY amount of 0.061 QALY (Rognoni & Gerzeli 2019). This value was near to score of 1, which meant complete health. Also, the healthcare system in Italy was excellent and had a high focus on heart failure treatment and patient compliance with therapy. The Markov study model was used to present the cost and outcomes together. This study also used the approach by Delphi to ask the clinicians about the clinical progress of the patients via e-survey (van Veldhuisen *et al.* 2017).

Furthermore, the lowest clinical outcome was in Spain with 0.335 QALY in FCM, with the incremental QALY being 0.037 QALY (Comín-Colet *et al.* 2015). South Korea had the lowest incremental QALY FCM compared with the placebo, with 0.021 QALY. This number could not be used to value the progress of patients' healthy functioning, as there was no data about QALY FCM after the incremental (Lim *et al.* 2014). However, it still indicated the quality-of-life improvement with FCM therapy. In all studies that presented the QALY index, ferric carboxymaltose was more cost-effective.

4.5 *Limitations of systematic review*

This systematic review could not make a comprehensive conclusion due to study heterogeneity and time horizon. The discount rate was not able to perform for these six studies, and using the CHEERS checklist to measure the study's quality was subjective.

5 CONCLUSIONS

The cost-effectiveness of ferric carboxymaltose for therapy in heart failure patients with iron deficiency is higher than placebo or without therapy, with the lowest FCM ICER value in seven studies being \$1,384/QALY in Italy and the highest in South Korea. The average ICER is \$7,814/QALY, with a median value of \$6,678/QALY.

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An overview of *Beta vulgaris L.*: Its functions as antidyplipidemia

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ABSTRACT: Dyslipidemia is a dysfunction of lipoprotein metabolism indicated by elevated total cholesterol, low-density lipoprotein, and triglyceride. Previous studies showed that lowering LDL levels greatly reduced the risk of morbidity and mortality from cardiovascular disease due to the atherosclerosis mechanism. This research aimed to pave the way for *Beta vulgaris L.* as a further pharmacological and nutritional agent for the prevention and treatment of dyslipidemia. This research used a systematic review method. Scopus, PubMed, and Science Direct from 2017 to 2022 were used to conduct a systematic review. This review focuses on the nutraceutical facts of *Beta vulgaris L.* as an alternative treatment for dyslipidemia in the future. The results showed *Beta vulgaris L.* juice had a significant positive effect on decreasing levels of fatty acid synthase, LDL, triglycerides, AST, and ALT and increasing HDL in human and animal experiments. *Beta vulgaris L.* leaf and stem extracts increased the protection of human endothelial cells from the oxidation process. This review showed the benefit of *Beta vulgaris L.* for improving lipid profile in dyslipidemia.

1 INTRODUCTION

Dyslipidemia is a global problem (Pirillo *et al.* 2021) and is closely linked to obesity, metabolic syndrome, atherosclerosis, coronary heart disease, increased susceptibility to cancer, and COVID-19 (Atmosudigdo *et al.* 2021). This condition is characterized by lipid disorders, including elevated low-density lipoproteins (LDL), high cholesterol, triglycerides, and low high-density lipoproteins (HDL) (Kopin & Lowenstein 2017). Dyslipidemia is a substantial risk factor for cardiovascular disease (Go *et al.* 2014). Numerous studies have shown that lowering LDL levels greatly reduces the risk of death and morbidity from atherosclerotic cardiovascular disease (Ren *et al.* 2010; Rodriguez-Colon *et al.* 2009). Cardiovascular morbidity and mortality can be changed substantially by controlling dyslipidemia. Statins are the cornerstone of the pharmacological treatment of dyslipidemia. However, using statins for a long term has negative effects, such as increased liver transaminases, muscle damage, excessive blood sugar, and cognitive impairment (Armitage 2007). Diet and lifestyle variables among the most important factors are used for dyslipidemia changes, therefore diet and lifestyle modifications are the main methods for treating dyslipidemia (Zeng *et al.* 2021).

In the last decade, many researches showed the use of a variety of natural remedies including active components that may alleviate dyslipidemia, and one of them was beetroot.

The beetroot is a commonly cultivated vegetable in the Americas, Europe, and Asia (Albasher *et al.* 2019) and is consumed regularly in our daily lives. In 2018, the expected global beetroot production was 275.49 million metric tons (Fu *et al.* 2020). The majority of beetroot is consumed as a vegetable (Desseva *et al.* 2020), although it is also consumed as juice (Desseva *et al.* 2020, Zamani *et al.* 2021) and can be processed as a food coloring agent (Wang *et al.* 2020). *Beta vulgaris L.* contains phytochemical compounds, such as betalains (Ninfali *et al.* 2017), nitrate (dos S. Baião *et al.* 2020), phenolic acids, and flavonoid (vitexin, rutin, apigenin, quercetin, orientin) (Platosz *et al.* 2020). All parts of this plant have beneficial health effects. This research aimed to pave the way for *Beta vulgaris L.* as a further pharmacological and nutritional agent for the prevention and treatment of dyslipidemia.

2 METHODS

2.1 Search strategy and study selection

A literature search was conducted covering Scopus, PubMed, and Science Direct. The key words included (“*Beta vulgaris L.*” OR beetroot) dyslipidemia, *Beta vulgaris L.*, and statin. This review reported articles published in English from 2017 up to 2022. After the search, all discovered citations were compiled and uploaded to Mendeley Reference Management Software, and duplicates were recognized.

2.2 Assessment of study quality

The inclusion criteria were research articles that used *Beta vulgaris L.* as a natural treatment. The subjects included an animal (rat) and humans with dyslipidemia. Dyslipidemia was diagnosed using criteria based on clinical laboratory parameters for the animal (Giknis & Clifford 2006) and the 2018 American Heart Association (AHA)/American College of Cardiology (ACC) Guideline on The Management of Blood Cholesterol (Grundy *et al.* 2019) for human. Animals and humans were considered to suffer from dyslipidemia when there was an enlargement in cholesterol total, triglyceride, LDL level, and lower HDL.

3 RESULTS AND DISCUSSION

A flow chart of the article-finding process and the total number of articles discovered is shown in Figure 1.

Systematic review studies help conclude whether or not to use *Beta vulgaris L.* for dyslipidemia treatment. *In vitro* experiments showed that the extract of beet leaves enhanced the oxidative protection of human endothelial cells against several oxidizing agents such as ox-LDL and H₂O₂. The protective effect of the extract against oxidative stress was not attributable to apigenin activity or its derivatives but rather to the activity of several bioactive chemicals found in the extract. In addition, the extract of beet leaves acted directly on reactive oxygen species (ROS) levels due to its high natural antioxidant content and synergistically activating and enhancing cellular defense against this sort of stress. The suppression of LDL oxidation *in vitro* and the negative effects of ox-LDL on endothelial cells indicated the possible use of this nontraditional meal as a functional diet for the adjunctive treatment of dyslipidemias (da Silva *et al.* 2020).

The high-fat diet (HFD) given to male Wistar rats derived from the modification of AIN-93G and AIN-93M, which included the addition of 60% calories, showed increased plasma cholesterol and triglyceride levels and liver damage. The effect of HFD was shown in histological changes in the liver and increased of liver transaminases (aspartate aminotransferase (AST), and alanine aminotransferase (ALT) (Gonzales-Barron *et al.* 2020; Sarna *et al.* 2016; Valenzuela *et al.* 2017). Giving 20 mg/kg of betanin (purified from fresh beet juice) for 20 days reduced triglycerides, AST, and ALT in the 60-day HFD group compared to the

80-day HFD group without betanin. Betanin treatment for 20 days reduced malondialdehyde (MDA) liver and lipid accumulation in hepatocytes (da Silva *et al.* 2019). In addition, Nadiya's research on high fat and fructose diet (HFFD) intervention in male Wistar rats for six weeks significantly increased serum fatty acid synthase (FAS) levels in the HFFD group. Giving beet substitution in 6%, 9%, and 12% levels showed lowered FAS relative gene expression levels (Nadiyah *et al.* 2021). Previous studies have shown that diets high in fat and fructose increase blood levels of FAS. However, diets containing beets can reduce their level by inhibiting the expression of the FAS gene. This effect may be related to the concentration of apigenin and luteolin in red beet. Apigenin can regulate lipolytic and lipogenic gene expressions and reduce the activity of enzymes responsible for hepatic triglyceride synthesis (Jung *et al.* 2016). On the other hand, luteolin can inhibit hepatic lipogenesis and lipid absorption, increase peroxisome proliferator-activated receptor gamma (PPAR γ) protein expression in adipose tissue, and increase its gene expression (Kwon *et al.* 2015).

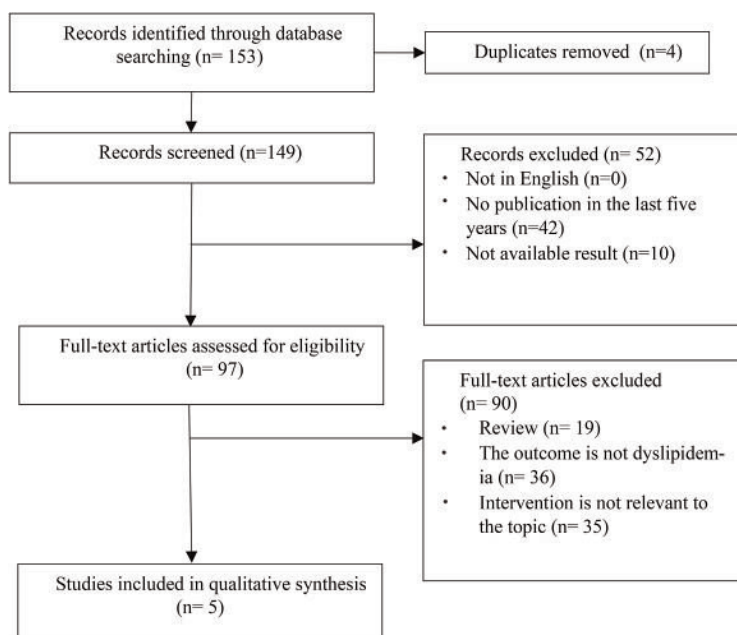


Figure 1. Article-finding process flow chart.

Research with human subjects included 13 participants given a high-fat meal consisting of a patty (fried dough) filled with pepperoni sausage, bacon, cheddar cheese, and coconut candy. Five minutes later, some participants were given a placebo while others were given beet leaf and stem juice. Fresh blood samples were collected 30, 60, 120, and 180 minutes after the initial sample. The results showed that a high-fat breakfast increased triglyceride levels after 120 and 180 minutes; moreover, giving beet leaf and stem juice could not inhibit triglyceride increase. Furthermore, reductions in HDL-C after 60,120, and 180 minutes were observed in the placebo group. These reductions were attenuated after 120 minutes in participants who received organic beet leaf and stem juice. Possibly due to the presence of vitexin-2-O-rhamnoside, a flavonoid glycoside produced from apigenin, beet leaf, and stem juice was able to mitigate the drop in HDL (Gomes *et al.* 2019). The presence of vitexin-2-O-rhamnoside in beet leaf and stem juice may have decreased the rise in cholesteryl ester transfer protein (CETP) activity generated by a high-fat meal, ultimately lowering the fall in HDL-C levels (Gomes *et al.* 2019). The other research conducted by Basaqr related to giving nitrate

supplements alone or nitrates with vitamin C to 13 people with criteria: LDL > 130 mg/dL caused a decrease in LDL and triglycerides but did not affect oxLDL and HDL. Nitrate supplements were available as a beetroot juice drink which contained an average dose of 400–450 mg of inorganic nitrate per 70 ml of concentrated beetroot juice (Kapil *et al.* 2015). Participants took concentrated beetroot juice seven days a week in the morning, followed one hour later by taking one of the capsules (vitamin C or placebo) for four weeks. Changes in plasma oxLDL and HDL were not significantly different when nitrate was administered alone or in combination with Vitamin C. The fasting lipid profile analysis revealed that the mean lipid alterations were substantially different for LDL and triglycerides between the two treatment groups. However, the purpose of this study was not to evaluate the benefits of vitamin C alone. Therefore, it was unknown if the systemic increase of nitric oxide from the combination of nitrate and vitamin C directly affected lipid and oxidative indicators or if vitamin C directly gave a favorable effect in this condition (Basaqr *et al.* 2021).

4 CONCLUSION

This systematic review showed that *Beta vulgaris L.* juice had a significant positive effect on decreasing levels of FAS, LDL, triglycerides, AST, and ALT and increasing HDL in human and animal experiments. *Beta vulgaris L.* leaf and stem extracts increased the protection of human endothelial cells from the oxidation process. This review showed the benefit of *Beta vulgaris L.* for improving lipid profile in dyslipidemia.

ACKNOWLEDGMENT

All author has reviewed and approved the final manuscript.

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Associated risk factors of raised D-dimer in COVID-19 patients with diabetes mellitus

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ABSTRACT: Abnormal coagulation function has been linked to the advancement of COVID-19 and diabetes mellitus (DM). However, the association of elevated D-dimer in COVID-19 patients with DM is unclear. This study aims to determine risk factors of raised D-dimer in COVID-19 patients with DM at Universitas Sebelas Maret Hospital. This retrospective study statistically analyzed the risk factors of 87 COVID-19 patients with DM who were admitted to Universitas Sebelas Maret Hospital from March 2020 to January 2021. Data were collected from patients' medical records. Binary logistic regression was applied to determine the association between potential variables on D-dimer. Among 87 patients, 70 had elevated D-dimer, while 17 had normal D-dimer. Age, admission oxygen saturation, patient outcome, newly diagnosed diabetic patients, admission plasma glucose levels and C-reactive protein (CRP) were significantly associated with D-dimer ($p = 0.017, 0.026, 0.001, 0.011, 0.036$ and 0.009 , respectively). However, increasing age (odds ratio [OR] 1.098 and 95% confidence interval [CI] 1.009 to 1.195; $p = 0.030$) was associated with an increased likelihood of D-dimer elevation, while newly diagnosed diabetic patients (OR 0.205, CI 0.052 to 0.806; $p = 0.023$) were associated with a reduced likelihood of D-dimer elevation in COVID-19 patients with DM. Older COVID-19 diabetic patients are prone to have higher levels of D-dimer. Therefore, they can be in a hypercoagulable state with a worse prognosis.

1 INTRODUCTION

On December 30, 2019, the primary cause of COVID-19 (Coronavirus Disease 2019) was found in Wuhan City, Hubei Province, China. This disease is caused by a novel coronavirus and was initially known as SARS-CoV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) but was eventually changed to COVID-19 by World Health Organization (WHO). This virus is transmitted from human-to-human through droplets, especially when people cough or sneeze. Currently, COVID-19 itself has widely spread from China to more than 190 other countries worldwide (Handayani *et al.* 2020; Susilo *et al.* 2020). The most frequently identified comorbidities in current COVID-19 patients are hypertension and diabetes mellitus (DM) (Osibogun *et al.* 2021; Surendra *et al.* 2021). COVID-19 patients with chronic diseases, such as DM and hypertension, have the worst outcome compared to other comorbidities and are frequently associated with acute respiratory distress syndrome (ARDS) and pneumonia (Sanyaolu *et al.* 2020).

DM has been one of the most consistent risk factors in COVID-19 patients with chronic disease, and uncontrolled hyperglycemia is always associated with poor prognosis and mortality

(Mishra *et al.* 2020; Surendra *et al.* 2021). This could happen because DM is also associated with other risk factors such as hypertension (Lestari & Ichsan 2020; Mishra *et al.* 2020). In addition, people with DM generally have irregular innate and adaptive immune responses and have low-grade chronic inflammation that makes them more susceptible to cytokine storms. Cytokine storms can occur when a person is infected with a new and highly pathogenic virus that causes uncontrolled cytokine production. People with DM may also be at greater risk for various thrombotic defects because DM is correlated with an imbalance between fibrinolysis and clotting factors (Lestari & Ichsan 2020; Lim *et al.* 2021; Mishra *et al.* 2020).

Patients with more severe clinical symptoms have higher D-dimer levels when compared to patients with milder clinical symptoms (Soni *et al.* 2020; Yao *et al.* 2020; Yu *et al.* 2020). D-dimer itself is a product of fibrin degeneration by plasmin. It is generally recognized as a biomarker for thromboembolic-related diseases and is also used as a prognostic marker for critically ill patients (Ou *et al.* 2021). D-dimer is also often used to assess the prognosis of various critical illnesses related to blood vessels, one of which is DM (Widjaja & Syahputra 2020).

This study provides information and references regarding associated risk factors of raised D-dimer in COVID-19 patients with DM to assist in determining the prognosis of these patients.

2 MATERIALS AND METHODS

2.1 Study design and population

A retrospective analysis was conducted on 87 patients hospitalized with COVID-19 and DM at Universitas Sebelas Maret Hospital from March 2020 to January 2021. The patient's positive diagnosis of COVID-19 was confirmed based on the reverse transcription-polymerase chain reaction (RT-PCR) results. Patients without admission plasma glucose levels and/or D-dimer examination within three days of admission are excluded from this research. Patients with pre-existing conditions such as pregnancy, venous thromboembolism, and anticoagulant usage history were also excluded. This research was conducted after earning ethical approval from the Health Research Ethics Commission of Dr. Moewardi Hospital with certificate number 394/III/HREC/2021.

2.2 Data collection

Demographic information, clinical data, and laboratory findings were collected from medical records. The laboratory findings used were the patient's plasma glucose levels at the time of admission and D-dimer presented on all included medical records, while neutrophil-lymphocyte ratio (NLR), c-reactive protein (CRP), creatinine, alanine transaminase (ALT), and aspartate transaminase (AST) were not presented on all research samples.

Blood samples were drawn on admission and sent to the hospital laboratory immediately. All measurements were done in the laboratory within 3 hours of sample collection. The D-dimer testing was done by latex turbidimetric immunoassay, and the result was expressed in ng/ml. Patients were then categorized into two groups based on their D-dimer levels according to the laboratory reference interval. A normal D-dimer range was defined as < 500 ng/ml. High level of D-dimer was defined as ≥ 500 ng/ml.

2.3 Statistical analysis

Continuous data were represented as median with interquartile range (IQR) or mean \pm standard deviation (SD) and were assessed using the Mann-Whitney U test or independent T-test depending on the normality. Categorical data were defined as the frequency with percentages and were evaluated using Fisher's exact test or Pearson's Chi-Square test where appropriate. A Kolmogorov-Smirnov test was also performed to test the normality of the data. Binary logistic regression was applied to define the correlation between potential variables on D-dimer. Possible variables were selected based on being statistically significant in

bivariate analysis. Statistical significance results are indicated by a p-value < 0,05. All analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA).

3 RESULTS

3.1 Baseline characteristics of COVID-19 patients with DM

The characteristics and laboratory findings of the cases are shown in Table 1. Patients' mean age was 55.55 ± 10.59 years, and 52.9% of patients were men, with the youngest being 27 years old and the oldest being 79 years old. Most patients (52.9%) had uncontrolled DM. No comorbidity was present in 46.0% of patients. The most prevalent comorbidities were hypertension (43.7%) and renal impairment (13.8%). A good prognosis was found in most cases (63.2%). 82.8% of patients had elevated plasma glucose levels upon admission. The Median D-dimer value was also elevated above the normal range (median and IQR at 854.57, 578 to 1597 mg/dl).

Table 1. Baseline characteristics of the study population and the association of clinical characteristics and laboratory findings between patients with normal and raised D-dimer.

Variables	n = 87	D-dimer <500 ng/ml (n = 17)	D-dimer ≥ 500 ng/ml (n = 70)	p	Zm
Clinical Characteristics					
Age (years), mean ± SD	55.55 ± 10.595	50.12 ± 9.18	56.87 ± 10.55	0.017*t	
Gender, n (%)					
Male	46 (52.9%)	11 (64.7%)	35 (50%)	0.276c	
Female	41 (47.1%)	6 (35.3%)	35 (50%)		
Admission oxygen saturation, median (IQR)	93 (88–97)	95 (93.5–98)	92 (83–97)	0.026*	–2.221
Pre-existing diabetes, n (%)					
Yes; controlled	8 (9.2%)	0	8 (11.4%)	0.346f	
Yes; uncontrolled	46 (52.9%)	6 (35.3%)	40 (57.1%)	0.105c	
Newly diagnosed diabetes, n (%)	33 (37.9%)	11 (64.7%)	22 (31.4%)	0.011*c	
Comorbidities, n (%)					
Hypertension	38 (43.7%)	6 (35.3%)	32 (45.7%)	0.437c	
Renal impairment	12 (13.8%)	1 (5.9%)	11 (15.7%)	0.446f	
Cardiovascular diseases	2 (2.3%)	0	2 (2.9%)	1.000f	
Stroke	3 (3.4%)	0	3 (4.3%)	1.000f	
Respiratory diseases	2 (2.3%)	1 (5.9%)	1 (1.4%)	0.354f	
None	40 (46.0%)	9 (52.9%)	31 (44.3%)	0.521c	
Previous diabetes therapies, n (%)					
Oral antidiabetic drugs	12 (13.8%)	0	12 (17.1%)	0.112f	
Insulin	7 (8.0%)	1 (5.9%)	6 (8.6%)	1.000f	
Not described	68 (78.2%)	16 (94.1%)	52 (74.3%)	0.104c	
Patient outcome, n (%)					
Cured and discharged	55 (63.2%)	17 (100%)	38 (54.3%)	<0.000-1**c	
Death	32 (36.8%)	0	32 (45.7%)		
Laboratory Findings					
Admission plasma glucose levels, n (%)					
Normal (≤ 140 mg/dl)	15 (17.2%)	0	15 (21.4%)	0.036*c	
Elevated (>140 mg/dl)	72 (82.8%)	17 (100%)	55 (78.6%)		
NLR, median (IQR) (n = 84)	4.54 (2.89–8.36)	3.8 (2.29–5.33)	5 (2.96–8.8)	0.136	–1.489
CRP (mg/L), median (IQR) (n = 30)	4.59 (1.32–11.49)	1.64 (0.145–3.545)	6.34 (2.78–12.37)	0.009*	–2.603
eGFR (ml/min/1.73m2), mean ± SD (n = 81)	82.35 ± 37.62	97.5 ± 34.42	78.62 ± 37.69	0.072t	
AST (U/L), median (IQR) (n = 54)	38.5 (23–51.5)	25 (19–47)	40 (25–57)	0.122	–1.547
ALT (U/L), median (IQR) (n = 53)	27 (18.5–40.5)	35 (14–44)	24 (18.75–36)	0.417	–0.812
D-dimer (ng/ml), median (IQR)	854.57 (578–1597)	383 (307.175–473.365)	1125.925 (770.555–2081.11)	<0.000-1**	–6.369

Older patients (56.87 ± 10.55 years vs. 50.12 ± 9.18 years; $p = 0.017$) with lower admission oxygen saturation (median 92 vs 95, and IQR 83 to 97 vs. 93.5 to 98; $p = 0.026$), and higher CRP (median 6.34 vs 1.64, and IQR 2.78 to 12.37 vs. 0.145 to 3.545; $p = 0.009$) were found to have high D-dimer. Most patients with normal D-dimer levels were newly diagnosed DM cases (64.7% vs. 31.4%, $p = 0.011$), thus they all had elevated admission plasma glucose levels (100% vs. 78.6%, $p = 0.036$). However, no death was found in patients with normal D-dimer levels (0% vs. 45.7%, $p < 0.001$).

3.2 Association between risk factors and D-dimer in COVID-19 patients with DM

Several risk factors were analyzed to determine their associations to D-dimer in COVID-19 patients with DM. Increasing age (odds ratio [OR] 1.098 and 95% confidence interval [CI] 1.009 to 1.195; $p = 0.030$) was associated with an increased likelihood of D-dimer elevation, and newly diagnosed diabetic patients (OR, 0.205, CI 0.052 to 0.806; $p = 0.023$) was associated with a reduced likelihood of D-dimer elevation in COVID-19 patients with DM (Table 2). Other risk factors had no significant effect on D-dimer.

Table 2. Independent predictors of raised D-dimer in COVID-19 patients with diabetes mellitus.

Variables	OR	95% CI	P
Ages	1.098	1.009–1.195	0.030*
Admission oxygen saturation	0.991	0.847–1.159	0.910
Patient outcome			
Cured and discharged	0.000	0.000	0.997
Death	1		
Newly diagnosed diabetes	0.205	0.052–0.806	0.023*
Admission blood glucose	0.997	0.997–1.003	0.998

OR, Odds Ratio; CI, Confidence interval.

*, significantly associated at p -value $< 0,05$

4 DISCUSSION

This study evaluated baseline characteristics and the association between potential risk factors and D-dimer in COVID-19 patients with DM. After controlling other variables, this study found that older and newly diagnosed diabetic patients are associated with D-dimer in COVID-19 patients with DM.

Previous studies found that COVID-19 enters the human body through ACE-2 receptors on multiple organs, such as the heart, liver, pancreas, kidney, etc. When SARS-CoV-2 binds to ACE-2 receptors, specifically on the pancreas, they damage the islet cells resulting in an elevation of plasma glucose levels (Vitiello & Ferrara 2020; Zhou *et al.* 2020). Furthermore, infectious conditions in diabetic patients can also cause the body to have difficulty controlling and managing the glycemic normalization (Li *et al.* 2020; Vitiello & Ferrara 2020; Zhou *et al.* 2020). Hyperglycemia is known to downregulate ACE-2 expression, making the cells more vulnerable to inflammation and increasing the damaging effect of the virus (Li *et al.* 2020; Zhou *et al.* 2020). Elevated glucose levels directly accentuate SARS-CoV-2 replication in human monocytes. The glycolysis process maintains SARS-CoV-2 replication through the generation of the activation of hypoxia-inducible factor 1-alpha and mitochondrial reactive oxygen species. As a result, hyperglycemia may promote viral replication (Lim *et al.* 2021).

Several literatures have discussed the relationship between COVID-19 patients and their history regarding DM. Newly diagnosed DM patients had higher mortality rates than those

with pre-existing DM and no diabetes-related COVID-19 (Li *et al.* 2020). This could happen because newly diagnosed DM patients often had elevated plasma glucose levels. Therefore, more severe clinical symptoms and higher inflammatory markers are found, and they are more susceptible to hyper inflammation, cellular damage, and respiratory failure (Farang *et al.* 2021; Li *et al.* 2020).

However, in this study, more newly diagnosed DM patients were discovered in the normal D-dimer group; thus, higher plasma glucose levels upon admission were acquired, yet none had poor outcomes. COVID-19 might trigger prediabetic patients to accelerate their disease progression into diabetic states due to the damaging process of islet cells (Barrett *et al.* 2022). We suggest that this accelerated process has not developed microvascular and macrovascular complications in newly diagnosed DM patients. Hence, the elevation of D-dimer might not be present at this stage. Further research regarding this matter is needed to confirm this suggestion.

We found that older age was significantly associated with D-dimer elevation in COVID-19 patients with DM. The aging process and DM are consistently correlated with endothelial dysfunction and inflammation-related pathway; therefore, could elevate D-dimer and are more susceptible to infections such as COVID-19 (Assar *et al.* 2016; Barrett *et al.* 2022; Engbers *et al.* 2010; Minuljo *et al.* 2020; Poudel *et al.* 2021).

Vascular endothelial dysfunction can promote microvascular complications among COVID-19 patients with DM. SARS-CoV-2 may enter endothelial cells through ACE-2 receptors resulting in apoptotic events of endothelial cells, infiltration of inflammatory cells, and promoting microvascular prothrombotic effect. Older people tend to have down-regulated inflammatory systems. Therefore, their response rate to infection is slower than younger people. This could enhance the development of the disease in a shorter period. Symptoms are only shown later in worse conditions leading to a worse prognosis (Assar *et al.* 2016; Engbers *et al.* 2010; Lim *et al.* 2021).

These were some limitations to this study. First, this study focuses solely on one hospital, hence lacking heterogeneity. Second, all data was acquired using patient's printed medical records. There were some laboratory findings, such as NLR, CRP, ALT, AST, and creatinine that were not completely present on all medical records as stated before. Therefore, we could not further analyse it in the multivariate analysis to determine their correlation with D-dimer. Third, other variables, such as symptoms and length of stay, should be considered and analyzed further.

Despite the limitations, this study also has several strengths. This is one of the first studies to specifically analyses COVID-19 in diabetic patients in Indonesia. Other studies often compare diabetic and non-diabetic patients, but this study focused solely on the characteristics and laboratory findings among diabetic patients, therefore making it more suitable to represent the diabetic population. We strictly chose our sample based on the exclusion and inclusion criteria, making the result more reliable.

5 CONCLUSION

In conclusion, our study identified several associated risk factors of D-dimer among COVID-19 patients with DM. Older COVID-19 diabetic patients are prone to have higher levels of D-dimer. Therefore, they can be in a hypercoagulable state with a worse prognosis.

ACKNOWLEDGEMENTS

The authors would like to express the greatest gratitude towards Faculty of Medicine, Universitas Sebelas Maret, Universitas Sebelas Maret Hospital, and Lembaga Penelitian dan Pengabdian Masyarakat (LPPM) Universitas Sebelas Maret for proving the support in completing the research. The authors declare no conflict of interest in this study.

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Association of mid-term blood pressure variability with in-hospital mortality in hypertensive COVID-19 patients

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ABSTRACT: Blood pressure variability is a biomarker that affects the clinical outcome of COVID-19 patients. COVID-19 patients with hypertension have a higher risk of death than patients without comorbidities. This study evaluates the relationship between blood pressure variability and in-hospital mortality in COVID-19 patients with hypertension. This study was an observational analytical study with a cross-sectional approach. This study analyzed 191 COVID-19 patients with hypertension who were administered to Sebelas Maret University Hospital from June 2020 to February 2022. Data were analyzed using logistic regression multivariate analysis and comparative analysis of independent T-test or Mann Whitney on numerical variables and Chi-Square test on categorical variables. $p < 0.05$ is considered significant. There was no significant relationship between blood pressure variability and in-hospital mortality in COVID-19 patients with hypertension from the multivariate analysis (SD SBP ($p = 0.620$), SD DBP ($p = 0.940$), CV SBP ($p = 0.868$), CV DBP ($p = 0.980$)). Meanwhile, there was a significant relationship between mean SBP ($p = 0.014$), age ($p = 0.018$) and admission oxygen saturation ($p < 0.001$) and in-hospital mortality. There was no significant relationship between blood pressure variability and in-hospital mortality of COVID-19 patients with hypertension.

1 INTRODUCTION

Since December 31, 2019, the world has been shocked by the emergence of a disease called COVID-19, which was first discovered in Wuhan, China. This disease is caused by a new type of coronavirus, officially named Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). WHO declared COVID-19 a global pandemic on March 11, 2020, because of its widespread in various countries in just a few moments and easily transmitted from person to person through droplets of saliva (Cucinotta & Vanelli 2020; Parasher 2021).

Several comorbid diseases such as hypertension (15.8%), cardiovascular and cerebrovascular diseases (11.7%), and diabetes (9.4%) increase the risk of infection, severity, and mortality in COVID-19 patients (Sanyaolu *et al.* 2020). COVID-19 patients with comorbid hypertension have a 2.2 times greater risk of death than patients without comorbid

hypertension. This is associated with the ACE2 (Angiotensin-Converting Enzyme 2) receptor, which binds to the SARS-CoV-2 virus to enter and replicate in the body. In hypertensive patients, ACE2 expression increases to prevent the accumulation of Angiotensin II making them more susceptible to COVID-19 infection (Wulandari *et al.* 2020).

The results of blood pressure measurements can vary due to physiological responses to environmental stimulation to maintain homeostasis. This change in blood pressure is known as variability. An increased blood pressure variability (BPV) that occurs continuously can indicate a pathological conditions (Rahtini & Widiana 2020). BPV can be an essential biomarker and influences the clinical outcome of COVID-19 patients (Li *et al.* 2021). Calculation of BPV is classified based on intervals into very short-term (beat-by-beat), short-term (within 24 hours), mid-term (day-by-day), and long-term (visit-to-visit) (Parati *et al.* 2013).

In their research, Nam *et al.* (2021) said that COVID-19 patients with hypertension and increased BPV as measured by the long-term (visit-to-visit) method were significantly associated with in-hospital mortality. High BPV has a higher risk of in-hospital mortality and admission to the Intensive Care Unit (ICU), so monitoring blood pressure in hospitalized patients is crucial (Ran *et al.* 2020). COVID-19 causes several mechanisms, such as systemic inflammation, decreased perfusion to the kidney, and interference with blood pressure regulation, thereby increasing BPV. Mehlum *et al.* (2018) found that visit-to-visit (long-term) BPV was associated with an increased risk of cardiovascular events and mortality.

Only now, research has yet to discuss the variability of mid-term (day-to-day) blood pressure with in-hospital mortality in COVID-19 patients with hypertension in Indonesia. Therefore, this research was conducted to help provide information and reference regarding the relationship between blood pressure variability and in-hospital mortality in COVID-19 patients with hypertension.

2 METHODS

2.1 *Research design and research sample*

This type of research is analytic observational with a cross-sectional approach. The research data were obtained from medical records. The population is COVID-19 patients with comorbid hypertension at UNS Hospital in June 2020-February 2022. Inclusion criteria include 1) patients diagnosed positive for COVID-19 based on RT-PCR examination results; 2) have a history of diagnosis of hypertension or who are taking or have ever taken antihypertensive drugs; 3) have blood pressure measurement data taken at least two times a day for five days since admission; 4) there is clinical outcome data of living/and/or deceased patients in the hospital.

Meanwhile, patients with hematological disorders, autoimmune diseases, cancer, patients receiving hemodialysis therapy, patients on mechanical ventilators at the time of admission, and patients with shock were excluded. The sampling technique used is total population sampling. Based on the sample size calculation, the minimum sample size was 143. In this study, 226 samples were obtained, but only 191 patients met the inclusion and exclusion criteria. This research has been approved by the Ethics Commission of RSUD Dr. Moewardi with Number 513/IV/HREC/2022.

2.2 *Blood pressure measurement*

The blood pressure measurement was used five days after admission, measured twice daily, in the morning and evening. The indicator of blood pressure variability in this study is illustrated by the calculation of the standard deviation (SD) of systolic blood pressure (SBP), and diastolic blood pressure (DBP) recorded on five consecutive days and the coefficient of variation (CV; SD divided by the average BP).

2.3 *Statistical analysis*

To compare baseline characteristics, we divided participants into two groups based on clinical outcomes: living and deceased patients. To compare the difference in mean scores

between the two clinical outcome groups, if the numerical data were normally distributed and homogeneous, the unpaired t-test was used; if not, then the Mann-Whitney test was used. An analysis of variables with categorical data was performed using the Chi-Square test. Binary logistic regression analysis examined the relationship between BPV and in-hospital mortality. All statistical analyzes were performed using the SPSS version 26 application.

3 RESULTS

3.1 Characteristics of research subjects

Table 1 shows that the mean age of the patients in this study was 55.52 years, with a standard deviation of 12.37. A total of 100 (52.4%) patients were male. Most of the patients (99.5%) had a GCS score of 15 (composmentis), and 75.4% of patients had an oxygen saturation level of $\geq 90\%$ at admission. There were 141 (73.8%) patients with comorbidities other than hypertension, and diabetes mellitus (39.8%) was the most common comorbid. The median length of stay in patients in this study was 11 days. As for the results of the laboratory examination of patients in this study, there was a median blood sugar value of patients at the admission of 136 mg/dl, NLR result is 4.61, SGOT has a median value of 32 U/L, SGPT has a median value of 24 U/L, and the median D-dimer number in the patients in this study was 865.57 ng/ml.

Table 1. Clinical characteristics of COVID-19 patients with hypertension.

Variable	Total (n = 191)	Clinical Outcomes		P value
		Live (n = 157)	Deceased (n = 34)	
Age (years), (mean \pm SD)	55.52 \pm 12.37	53.97 \pm 15.32	60.15 \pm 11.96	0.016 ^{T*}
Gender				
Male	100 (52.4%)	83 (52.9%)	17 (50%)	
Female	91 (47.6%)	74 (47.1%)	17 (50%)	
GCS (n (%))				0.031 ^{S*}
15	190 (99.5%)	157 (100%)	33 (97.1%)	
<15	1 (0.5%)	0 (0%)	1 (2.9%)	
Admission O2 saturation (n (%))				<0.001 ^{S*}
≥ 90	144 (75.4 %)	133 (84.7%)	11 (32.4%)	
<90	47 (24.6%)	24 (15.3%)	23 (67.6%)	
Other comorbidities (n (%))				
Diabetes mellitus	76 (39.8%)	58 (37%)	18 (52.9%)	
Impaired kidney function	36 (18.8%)	26 (16.6%)	10 (29.4%)	
Cardiac disease	66 (34.6%)	54 (34.4%)	12 (35.3%)	
Without other comorbidities	50 (26.2%)	46 (29.3%)	4 (11.8%)	
Long hospital stays (days)	11 (5–33)	10.5 (5–21)	9 (5–33)	0.013 ^{M*}
Admission blood sugar (mg/dl)	136 (33–1189)	137 (93–227)	138 (33–649)	0.782 ^M
Neutrophil-Lymphocyte Ratio	4.61 (12–33.82)	3.81 (0.98–19.55)	8.02 (1.21–33.82)	<0.001 ^{M*}
AST (SGOT) (U/L)	32 (8–264)	35 (17–101)	38.5 (12–1127)	0.028 ^{M*}
ALT (SGPT) (U/L)	24 (5–152)	30 (5–112)	21 (6–118)	0.671 ^M
D-dimer (ng/ml)	865.57 (33.5–10000)	700.16 (199.02– 4016.67)	1443.97 (580.33– 7844.3)	<0.001 ^{M*}

Abbreviations: SD, standard deviation; ^T T-Test; ^S Chi Square; ^M Mann-Whitney; Min, Minimal; Max, Maximal; *significant p<0.05

Table 1 also shows a bivariate comparative analysis of each variable on patient clinical outcomes. Comparison between groups showed significant results for age ($p = 0.016$), GCS ($p = 0.031$), oxygen saturation at admission ($p < 0.001$), length of stay ($p = 0.013$), Neutrophil-Lymphocyte Ratio (NLR) ($p < 0.001$), SGOT ($p = 0.028$), and D-dimer ($p < 0.001$). Meanwhile, there were no significant differences in sex, admission blood sugar, and SGPT results.

3.2 Comparison of blood pressure variability

Table 2 shows the blood pressure's absolute, SD, and CV values. There was a difference in mean SD SBP ($p = 0.021$) in patients with clinical outcomes of life and death.

Table 2. Comparison of blood pressure variability in COVID-19 patients with clinical outcomes of living and deceased patients.

Variable	Total (n = 191)	Clinical Outcomes		P values
		Live (n = 157)	Deceased (n = 34)	
SBP (mmHg)	138.78 (115.8–194.4)	133.14 (116.6–180.2)	142.61 (122.4–178.7)	0.021^{M*}
DBP (mmHg)	82.86 ± 8.80	82.06 ± 10.42	82.71 ± 9.40	0.916 ^T
Systolic Variability				
SD SBP (mmHg)	16.85 ± 5.67	17.15 ± 5.77	17.29 ± 6.24	0.622 ^T
CV SBP (%)	12.02 ± 3.86	12.43 ± 3.79	11.92 ± 4.13	0.869 ^T
Diastolic Variability				
CV DBP (%)	10.44 ± 4.35	11.42 ± 5.03	10.38 ± 3.54	0.940 ^T
SD DBP (mmHg)	12.60 ± 4.99	13.76 ± 5.20	12.62 ± 4.36	0.980 ^T

Abbreviations: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; SD, Standard Deviation; CV, Coefficient of Variation; ^a T-Test; ^c Mann-Whitney; *significant $p < 0.05$

3.3 Relationship between blood pressure variability and in-hospital mortality in COVID-19 patients with hypertension

Table 3 presents the logistic regression analysis results of in-hospital mortality according to the independent variables. The independent variables systolic blood pressure (SBP), diastolic blood pressure (DBP), BPV (SD SBP, SD DBP, CV SBP, and CV DBP), and age were analyzed in the form of continuous variables. Meanwhile, the variables GCS (0 = 15; 1 = <15), oxygen saturation at admission (0 = <90; 1 ≥90), and comorbid diseases (0 = no; 1 = yes) were analyzed in the form of nominal variables. There was a significant effect in mean SBP ($p = 0.014$), age (0.018), and O₂ saturation at admission (< 0.001) on in-hospital mortality.

Table 3. In-hospital mortality logistic regression results according to several independent variables.

Variable	Wald	P value	B	OR
SBP	5.231	0.014	0.041	1.042
DBP	0.011	0.916	-0.002	0.998
Systolic Variability				
SD SBP	0.246	0.620	0.016	1.016
CV SBP	0.028	0.868	-0.008	0.992
Diastolic Variability				
SD DBP	0.006	0.940	-0.003	0.997
CV DBP	0.001	0.980	0.001	1.001
Age	5.618	0.018	0.052	1.054
GCS	2.505	0.113	-0.503	0.604
Admission O ₂ saturation	32.695	<0.001	-2.337	0.097

(continued)

Table 3. Continued

Variable	Wald	P value	B	OR
Other Comorbidities				
Diabetes Mellitus	2.928	0.087	-0.652	0.521
Impaired Kidney Function	2.929	0.087	-0.742	0.476
Cardiac Disease	0.010	0.920	0.040	1.040
Without other comorbidities	4.094	0.211	1.134	3.108

Abbreviations: B, regression coefficient; OR, odds ratio

4 DISCUSSION

Based on Table 3, this study shows that several independent variables have a significant effect on the dependent variable as evidenced by the coefficient values of each variable, namely:

4.1 Mean systolic blood pressure

The average systolic blood pressure (SBP) variable produces odds ratio 1.042 which means that this variable is a determining factor of in-hospital mortality. This is in line with a study by Caillon *et al.* (2021) that the average SBP in the group of patients who died was higher than that of patients who recovered from COVID-19. The higher average SBP can be caused by uncontrolled hypertension. There is also a possibility that the increase in SBP is caused by the binding between SARS-CoV-2 and ACE2, which causes a decrease in ACE2 enzyme activity resulting in an imbalance between Ang-II and Ang 1-7 (Schiffrin *et al.* 2020).

4.2 Age

The odds ratio value for the age variable is 1.05, influencing the hospital's mortality probability. This is in line with research which showed age increased the mortality risk 1.079 times and 1.03 times for COVID-19 patients (Albitar *et al.* 2020; Barman *et al.* 2021). Older age tends to have several comorbid diseases and lower immunity levels. Using some drugs due to comorbid illnesses can cause adverse reactions because of decreased organ function (Biswas *et al.* 2021). Aging causes a decrease in the function of CD4+, CD8+ and B cells, so the immune response to viral infections becomes disrupted (Dessie & Zewotir 2021). In addition, ACE2 expression decreases with age. Decreased ACE2 receptor activity causes Ang-II cannot be converted into Ang 1-7, and this imbalance triggers inflammation so it has a worse prognosis. (Angeli *et al.* 2021)

4.3 Patient's oxygen saturation at admission

The odds ratio value of the oxygen saturation (SpO₂) variable at admission is 0.097, it influences the probability of mortality in the hospital. The same happened in a study by AbuRuz *et al.* (2022), where lower SpO₂ was significantly associated with a higher death rate. The study stated that less than 94% of SpO₂ was considered a cause of patient death. COVID-19. Research conducted by Du *et al.* (2020) states that SpO₂ at admission predicts the prognosis of COVID-19 patients. A decrease in SpO₂ is a marker of lung damage, worsening disease, and death. The release of cytokines as the body's inflammatory response to SARS-CoV-2 caused alveolar inflammation and decreased surfactant production, thereby accelerating hypoxemia. Low SpO₂ increases viral replication, exacerbates inflammation and further worsens hypoxemia, which risks mortality due to COVID-19 (Asleh *et al.* 2021; Jiang Xie 2020; Tomas Kara; Virend K. Somers).

Based on the results of multivariate analysis in this study, where analysis between blood pressure variability (SD SBP, SD DBP, CV SBP, and CV DBP) with confounding variables (age, GCS, admission oxygen saturation, and comorbidities) on in-hospital mortality, no significant relationship was found in the BPV variable on the in-hospital mortality of COVID-19 patients at the UNS Hospital because the significant value on the Wald test was >0.05 . Meanwhile, there was a significant relationship between TDS ($p = 0.014$), age ($p = 0.018$), and admission SpO₂ ($p < 0.001$) to in-hospital mortality.

In contrast to this study, a study conducted by Nam *et al.* (2021) showed that there was a significant relationship between increased systolic and diastolic BPV and in-hospital mortality in COVID-19 patients with a p -value < 0.001 and a hazard ratio of 1.617 with using the Cox proportional hazard regression multivariate test. The difference could be because this study used SD as a parameter for calculating BPV, whereas Nam *et al.* (2021) use MAP (Mean Arterial Pressure) as a parameter of BPV. This study cannot use MAP as a parameter because it uses day-to-day blood pressure data so the parameters that can be used are SD and CV, while MAP is used in blood pressure data for 24 hours (short-term).

Research conducted by Li *et al.* (2021) showed that the variability of systolic blood pressure (SD SBP) was significantly associated with worse clinical outcomes using logistic regression analysis with $p = 0.02$ and odds ratio 3.41. The difference in the analysis results could be due to research by Li *et al.* (2021) that measured blood pressure once a day in the morning for 3-47 days, whereas in this study measured twice a day in the morning and evening for five days. Increasing the time interval between blood pressure measurements will increase BPV because the data obtained is small. This is different if the time interval between blood pressure measurements is short, then more data will be obtained causes the BPV to decrease.

Another factor that may influence the difference in the results of this study used logistic regression analysis, while several studies on in-hospital mortality in COVID-19 patients used Cox proportional hazard regression analysis as was done by Ran *et al.* (2020), Caillon *et al.* (2021), and Li *et al.* (2021). Cox proportional hazard regression analysis is a survival analysis using the dependent variable in the form of survival time, while the dependent variable in the logistic regression analysis is nominal. Research conducted by Caillon *et al.* (2021) uses a survival time of 40 days, Li *et al.* (2021) uses 47 days, and Ran *et al.* (2020) uses 39 days.

This is a unicentric research and cross-sectional study, which only collect existing data without further follow-up of patients. This study also did not differentiate between hypertensive patients who were newly diagnosed with hypertension while receiving hospital treatment and those who were already receiving treatment. To determine the relationship between BPV and in-hospital mortality, further studies with larger study groups and multicentric studies with data obtained from various hospitals are still needed.

5 CONCLUSION

Based on the results of a study of 191 COVID-19 patients at UNS Hospital, it can be concluded that there is no significant relationship in the blood pressure variability variable to in-hospital mortality of COVID-19 patients at UNS Hospital who were treated from June 2020 to February 2022.

ACKNOWLEDGEMENT

The authors would like to express the greatest gratitude towards Faculty of Medicine, Universitas Sebelas Maret, Universitas Sebelas Maret Hospital, and Lembaga Penelitian dan Pengabdian Masyarakat (LPPM) Universitas Sebelas Maret for proving the support in completing the research.

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Comprehensive review in psychosis of Parkinson disease: Pathophysiology, best therapy, and prognosis

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ABSTRACT: Among the non-motor symptoms of Parkinson disease (PD), psychosis is one of the most common, complex, and disabling non-motor symptoms, with an estimated prevalence of up to 43–63% in the advanced stages of PD. The prevalence of psychosis in PD increases as the disease progresses and is associated with poorer quality of life, disability, and increased caregiver stress, as well as increased cognitive decline, hospitalization rates, morbidity, and mortality. Psychosis not only occurs naturally in the disease progression but is also caused by PD medication itself, dopamine-related therapy. Numerous literary works discuss the fundamentals of treating psychosis in PD, which also includes using anti-psychotic drugs such as pimavanserin, clozapine, and quetiapine. Our group reviewed literature specifically about psychosis in PD. Key topics include the pathophysiology of psychosis in PD, the causal mechanism of psychosis by PD medication, and also the best principle of therapy in patients with psychosis in PD. Psychosis in PD has become a unique challenge for clinicians to overcome how PD medication can become the cause of psychosis, so this raises questions and directions for future research to come.

1 INTRODUCTION

Parkinson disease (PD) is a neurodegenerative condition known to be accompanied by the death of dopaminergic neurons. Numerous hypotheses have been put up to date to explain the pathophysiology of PD (Balestrino & Schapira 2020; Kouli *et al.* 2018; Riederer *et al.* 2019). The possibility of α -synuclein protein misfolding is one well-known idea (Kouli *et al.* 2018; Riederer *et al.* 2019). The subsequent step involving chaperones and ubiquitin to destroy this misfolded protein is exceedingly challenging. In this manner, α -synuclein aggregates from an initial monomer to an oligomer and then to a Lewy body (Kouli *et al.* 2018).

This review is a narrative review that pays greater attention to pathophysiology and even includes a chart to help readers grasp it because there are still many people who do not fully comprehend psychosis in Parkinson's, particularly its pathogenesis.

2 METHODS

This narrative review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Page *et al.* 2021). A systematic search was carried out in October 2022 using PubMed, NCBI, ResearchGate, and Scopus databases about psychosis in Parkinson disease focusing in pathophysiology, anatomical pathogenesis, dopamine therapy, recent treatment update, and prognosis. We used the following keywords: “psychosis”, “Parkinson disease”, “Lewy bodies”, “ventral tegmentum

area”, “pimavanserine”, “dopaminergic pathway”, “substantia nigra pars compacta”, and “dopamine therapy”.

Studies were included if they met the following criteria: 1) topic related to psychosis in Parkinson disease in English; 2) article from 2018–2022; 3) treatment guidelines of psychosis in Parkinson disease related to dopamine agonist; 4) treatment of psychosis in Parkinson disease related to pimavanserine. The following exclusion criteria were used: 1) studies in languages other than English; 2) narrative reviews; 4) animal studies; 5) post-mortem studies.

3 RESULTS

3.1 *Psychosis of Parkinson disease*

Lewy body attaches to dopaminergic neurons in substantia nigra pars compacta (SNc), then continuous oxidative stress occurs and ends with the death of the dopaminergic neuron cells (Trist *et al.* 2019). It should also be noted that the ventral tegmentum area (VTA) also includes sites in the midbrain that produce dopamine. However, the dopamine produced by the VTA is projected chiefly in the cortex and limbic areas (Trutti *et al.* 2019).

It is known that under normal conditions, dopamine is needed in all parts of the brain, only that each part has different dopamine receptors (Olanow *et al.* 2020). There are two main groups of dopamine receptors: the D1 receptor family and the D2 receptor family. The D1 receptor family consists of D1 and D5 receptors. In the D2 receptor family, there are D2, D3, and D4 receptors. These receptors have different portions in each part of the brain (Mishra *et al.* 2018).

3.2 *Dopamine pathway*

Following the release of dopamine from dopaminergic neurons, it is transported through four pathways: nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular (Figure 1) (Latif *et al.* 2021). Since the nigrostriatal pathway is involved in motor function, two motor symptoms of Parkinson’s disease: bradykinesia and stiffness, will emerge clinically if dopamine levels are low (Quattrone *et al.* 2018). Dopamine disruptions in the mesolimbic route can result in positive symptoms like psychosis (McCutcheon *et al.* 2019), whereas dopamine disturbances in the mesocortical pathway can result in negative symptoms like depression and cognitive decline (Jenner *et al.* 2020). Dopamine abnormalities in the tuberoinfundibular pathway can result in hyperprolactinemia, which is linked to amenorrheal and galactorrhea symptoms (Choi & Horner 2019).

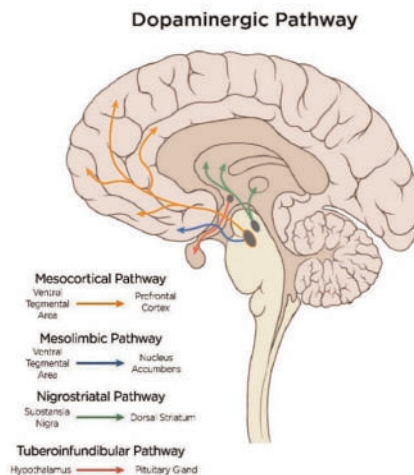


Figure 1. Dopaminergic pathway.

3.3 Dopamine relationship in cortex, striatum, and midbrain

Dopamine is a neurotransmitter known to be necessary for all regions of the brain where there is an interregional connection. Figure 2 illustrates how the cerebral cortex influences the VTA's ability to release dopamine (Latif *et al.* 2021). The 5HT2A receptors in the visual, temporal, motor, and prefrontal cortex increase GABA before activating glutamate receptors. The VTA, a dopaminergic neuron, is then stimulated by glutamate to produce dopamine. Additionally, dopamine travels down the mesolimbic route before reaching the ventral striatum (Cummings *et al.* 2022). The nigrostriatal pathway, which originates from the substantia nigra pars compacta, transports dopamine to the dorsal striatum (Figure 2) (Martín-Bastida *et al.* 2019).

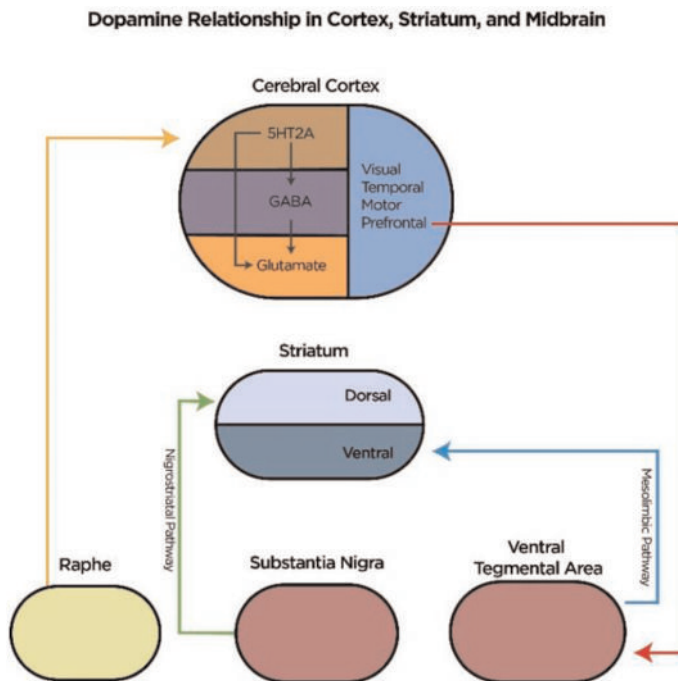


Figure 2. Dopamine relationships in the cortex, striatum, and midbrain [modified from (Stahl 2016)].

3.4 Psychosis and lewy bodies

Psychosis in Parkinson disease is one of the most common non-motor symptoms, is complex, and causes disability, with an estimated prevalence of up to 43–63% in the advanced stages of Parkinson's disease (Chendo *et al.* 2022). The prevalence of psychosis in Parkinson's disease increases with age. Disease progression is associated with poorer quality of life, disability, and increased caregiver stress, as well as increased cognitive decline, hospitalization rates, morbidity, and mortality (Eichel *et al.* 2022).

Previously described how Lewy bodies formed in PD, these Lewy bodies not only accumulate in the SNc but also accumulate in the cortex. With the presence of Lewy bodies in the cortex, it will cause 5HT2A activity to increase. As a result, more glutamate is produced (Kung *et al.* 2018). Thus, the VTA releases more dopamine through the mesolimbic than through the ventral striatum. An overactive mesolimbic pathway and ventral striatum can

produce symptoms of psychosis (Theis *et al.* 2021). Even the opposite occurs in the dorsal striatum. The dorsal striatum receives only a few amounts of dopamine from the SNC due to the accumulation of Lewy bodies in the SNc. So in this condition, there are parkinsonian motor symptoms with psychosis (Figure 3) (Carmichael *et al.* 2021).

Symptoms of psychosis that appear in PD are generally in the form of hallucinations and delusions (Lenka *et al.* 2019). In contrast to other primary psychotic illnesses, visual hallucinations are more common than auditory and tend to occur in the late afternoon or dimly lit environments. The delusions that appear are more of persecution or jealousy (Stahl 2018; Kataoka & Sugie 2018).

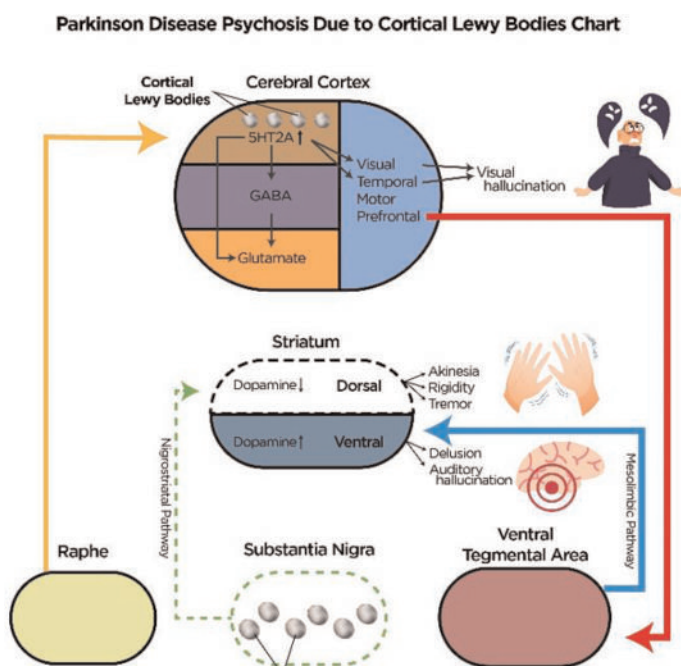


Figure 3. The pathophysiology of psychosis due to Lewy bodies [modified from (Stahl 2016)].

3.5 Psychosis due to dopamine therapy

Psychosis in PD can also be caused by dopamine-related therapy (Figures 4–5) (Angelopoulou *et al.* 2022). Levodopa and dopamine agonists are recently the drugs of choice for Parkinson’s disease (Armstrong & Okun 2020). After crossing the blood-brain barrier, Levodopa will then be converted into dopamine. This dopamine then binds to dopamine receptors, which are expected to occur at dopamine receptors in the dorsal striatum, resulting in an improvement in motor symptoms in PD (Raza *et al.* 2019). But in reality, this dopamine will also bind to its receptors in the ventral striatum, resulting in excess dopamine in the ventral striatum then psychotic symptoms may appear (Stahl 2018).

Dopamine agonists are currently used primarily in patients with Parkinson’s disease under 60 years of age (Latt *et al.* 2019). Dopamine agonists, such as pramipexole, have a high affinity for the D3 receptor, which is most abundant in the nucleus accumbens (limbic) and ventral striatum regions (Jiang *et al.* 2021). So the administration of dopamine agonists such as pramipexole can cause symptoms of psychosis.

Parkinson Disease Psychosis Due to Dopamine Agonists Chart

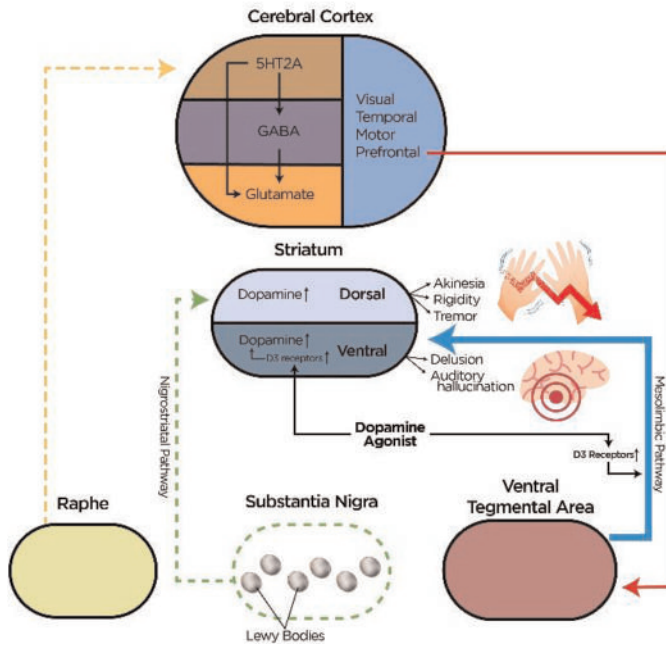


Figure 4. Psychosis due to dopamine agonist therapy [modified from (Stahl 2016)].

Parkinson Disease Psychosis Due to L-DOPA Chart

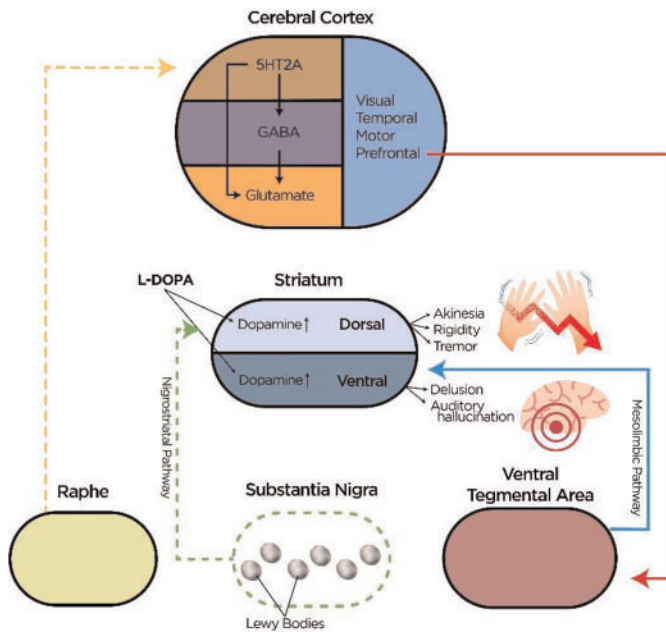


Figure 5. Psychosis due to Levodopa therapy [modified from (Stahl 2016)].

3.6 Psychosis therapy in Parkinson disease

The principle of management of psychosis in Parkinson disease includes the following stages (Table 1).

Table 1. Principles of managing psychosis in Parkinson’s disease (Rissardo *et al.* 2022; Taddei *et al.* 2017).

Principal	Therapy
I General adjustments	Circadian rhythm adjustment Adjustment of sensory input to normal level Use of hearing and vision aids
II Management of trigger factors	Adjustment of living and family environment Management of infection, dehydration Monitor electrolyte balance, glucose, vitamins, and hormones Management of heart failure
III Elimination of non-essential drugs	Eliminate the use of anticholinergics, anti-glutamatergic, sedative drugs
IV Reduction of anti-parkinsonian drugs	Dose reduction starts with anticholinergic → amantadine → MAO-B inhibitor → dopamine agonist → COMT-inhibitor → L-dopa retard → nonretarded L-dopa
V Cholinesterase inhibitors in patients with cognitive impairment	Rivastigmine 6–12 mg/day in 2–3 divided doses/day Donepezil 5–10 mg/day 1 dose/day Galantamine 4–32 mg/day divided by 2–3 doses/day
VI Antipsychotic drugs	Pimavanserin 34 mg/day Clozapine 12.5–62.5 mg/day Quetiapine 12.5–75 mg/day

Pimavanserin is a selective inverse agonist of the serotonin 5-HT_{2A} receptor without dopaminergic, adrenergic, histaminergic, or muscarinic affinity. Pimavanserin is the first and is currently the only drug to treat psychotic symptoms in Parkinson’s disease that has been approved by the FDA since 2016; and is based on the guidelines for psychosis in Parkinson’s disease issued by The International Parkinson and Movement Disorder Society (MDS) in 2018, the practical implications of this drug are categorized as clinically useful (Hu *et al.* 2020). Pimavanserin can significantly reduce the frequency and severity of hallucinations and/or delusions in Parkinson’s patients with psychosis (Isaacson & Citrome 2022). Side effects are found in about 5% of patients with symptoms such as nausea, peripheral edema, confusion, constipation, and gait disturbances (Cusick & Gupta 2020). This drug is given orally as much as 2 pills (17 mg each) once a day with a total dose of 34 mg/day (Davis *et al.* 2021). The FDA does not recommend this drug to be given to elderly patients with dementia, especially those receiving cholinesterase inhibitors, because it can increase the risk of mortality (Espay *et al.* 2018).

Clozapine and quetiapine are dopamine D₂ and serotonin 5HT_{2A} receptor antagonists with a high affinity for serotonin 5HT_{2A} receptors (Ceskova & Ceskova 2022). Both of these drugs can reduce the symptoms of psychosis in Parkinson’s patients including pimavanserin, but there are some things to watch out for. Although clozapine is categorized as clinically beneficial in the guidelines issued by the MDS, this drug is seldom used because it requires frequent blood tests due to the risk of agranulocytosis (Dashtipour *et al.* 2021). Meanwhile, quetiapine is categorized as possibly useful because research evidence is lacking so its efficacy is low (Seppi *et al.* 2019). Quetiapine might be recommended when pimavanserin is contraindicated or unavailable, as quetiapine does not exacerbate motor symptoms at low doses, with regular monitoring for side effects such as somnolence and orthostatic

hypotension (Williams *et al.* 2022). As for other antipsychotics, both typical and atypical (such as olanzapine, risperidone, and aripiprazole), MDS and the investigators agreed to avoid their use because of the high tendency to worsen motor symptoms due to dopamine receptor blockade (Phuong *et al.* 2021; Pahwa *et al.* 2022).

3.7 Psychosis prognosis in Parkinson disease

Psychosis symptoms in Parkinson's disease can be controlled with a good therapeutic approach, such as the management of trigger factors and modification of Parkinson's drug regimens to the administration of atypical antipsychotics (Simonet *et al.* 2020). So generally, the prognosis of psychosis in Parkinson's disease is good. However, in Parkinson's patients with dementia, the use of atypical antipsychotics can increase the risk of falls, cognitive deterioration, pneumonia, cardiovascular disorders, stroke, and death (Phan *et al.* 2019).

4 DISCUSSION

Upregulated 5HT_{2A} receptors in the cerebral cortex, which are thought to be caused by cortical Lewy body deposition, are linked to psychosis in Parkinson's Disease and may theoretically trigger a serotonin-dopamine imbalance syndrome that is characterized by visual hallucinations and delusions. According to the theory that serotonin and dopamine neurotransmitter systems have been restored to equilibrium, blocking 5HT_{2A} receptors enhances PDP without increasing motor symptoms. Therapy for psychosis in Parkinson Disease should become a particular concern for us which consist of general adjustments, management of trigger factors, elimination of non-essential drugs, reduction of anti-parkinsonian drugs, cholinesterase inhibitors in patients with cognitive impairment, anti-psychotic drugs. Pimavanserin will probably be useful in treating Lewy body dementia's visual hallucinations because 5HT_{2A} receptors are likewise activated in dementia with Lewy bodies.

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Creatinine and blood urea nitrogen levels in relation to Mortality rates of COVID-19 patients

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ABSTRACT: Coronavirus disease 2019 (COVID-19) is a contagious, life-threatening infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The SARS-CoV-2 virus enters the human body by binding to the ACE2 (Angiotensin-Converting Enzyme 2) receptor. ACE2 is expressed in various human organs such as the heart, kidneys, brain, and lungs. This is thought to be the cause of organ failure in many cases of COVID-19, especially in the kidney. The most frequent examination of kidney function is the examination of creatinine levels and blood urea nitrogen (BUN). Recent research suggests that creatinine and BUN levels are more likely to rise during COVID-19 infection. Only a few studies, in several countries, have shown that there is a relationship between creatinine and BUN levels with an increased mortality rate in patients with COVID-19. Due to the lack of research, this study aims to find out if there is a significant correlation between creatinine and BUN levels with the COVID-19 mortality rate. This study was done using an analytic observational method through a cross-sectional approach to 116 confirmed COVID-19 patients in Sebelas Maret University Hospital, Surakarta, Indonesia, as samples. From our analysis using the chi-square test, we have obtained a creatinine-mortality rate result of $0.020 < 0.050$ ($p\text{-value} = 7.844 > 5.991$, contingency coefficient $C = 0.252$, Odds Ratio (OR) = 0.532), and a BUN-mortality rate result of $0.000 < 0.050$, ($p\text{-value} = 7.844 > 5.991$, contingency coefficient $C = 0.381$, and Odds Ratio (OR) = 0.183). Finally, it can be concluded that there is a significant relationship between creatinine and BUN levels with the mortality rates of COVID-19 patients at Sebelas Maret University Hospital.

1 INTRODUCTION

1.1 *Virus transmission and epidemiology*

At the beginning of 2020, the world was shocked by the outbreak of a new virus, named the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the disease is called Coronavirus disease 2019 (COVID-19). This virus was first reported from Wuhan, China, at the end of 2019 and continues to grow rapidly around the globe, so that on January 30, 2020, the disease was declared a Public Health Emergency of International Concern (PHEIC) (Taheri *et al.* 2021; Tezcan *et al.* 2020). Found at the end of December 2019, until mid of 2022, many countries have been infected with COVID-19. WHO declared this disease a pandemic on March 11, 2020 (WHO 2020).

According to the data from the WHO, in mid-March 2022, there were a total of 64,809,377 confirmed cases of COVID-19 globally, with a total number of global deaths due to COVID-19 infection is 6,062,536. Many countries have become targets of COVID-19 infection, especially Indonesia. In mid-March 2022, there were 5,948,610 million cases of COVID-19 infection with a death rate of more than 150 thousand people, in Indonesia.

Various studies explain that COVID-19 can spread through droplet transmission, direct contact, and aerosols (World Health Organization 2020). The SARS-CoV-2 virus then enters the human body by binding to the ACE2 (Angiotensin-Converting Enzyme 2) receptor. ACE2 is expressed in various human organs such as the heart, kidneys, brain, and lungs. This is thought to be the cause of organ failure in many cases of COVID-19. In the kidney, ACE2 receptors are expressed in the apical brush border of the proximal tubule and in podocytes (Fabrizi *et al.* 2020).

1.2 COVID-19 pathophysiology, clinical manifestations, and prognosis

The virus efficiently binds to the angiotensin-converting enzyme 2 (ACE2) receptor which can be expressed in many organs including the bronchi and lung parenchyma, heart, kidney, and gastrointestinal tract. Research conducted by Zhao *et al.* (2020) demonstrated that ACE2 was highly expressed in alveolar type II epithelial cells, suggesting that these cells may be a specific reservoir for viruses. The viral RNA will be translated into the host cell (translation), replicated, transcribed, synthesized in its body structure, assembled into new cells with the host cell membrane, and finally released into the host body with the help of E, M, and N proteins (Mousavizadeh & Ghasemi 2021; Pei *et al.* 2020). Other studies have shown that ACE2 cells have several genes related to viral development processes, such as replication, life cycle, and assembly into cells, thereby facilitating viral replication in the lungs (Benedetti *et al.* 2020).

After binding to ACE2, the transmembrane protease serine 2 (TMPRSS2) mediates the priming of protein S and allows the virus to enter the host cell via clathrin-dependent endocytosis (Benedetti *et al.* 2020). The interaction of the SARS-CoV-2 virus in the host cell will affect 4 things. First, the direct SARS-CoV-2 virus has an immediate effect after binding directly to the ACE2 receptor. Second, through dysregulation in the RAAS system. ACE2 functions to break down angiotensin I into angiotensin 1-9 and break down angiotensin II into angiotensin 1-7 (Ahmadian *et al.* 2021; Nadim *et al.* 2020). If the ACE2 receptor binds to the SARS-CoV-2 virus, the breakdown of angiotensin I and II will be reduced, so that the protective function of the kidney will be inhibited and increase the effects of angiotensin II such as vasoconstriction, tissue injury, vascular permeability, thrombosis, and increased proinflammatory cytokines in the body. Third, it also causes damage to endothelial cells and thrombo-inflammation. ACE2 receptors found in arterial and venous endothelial cells bind to the SARS-CoV-2 virus. This will activate neutrophils, and macrophages, and reduce the von Willebrand factor resulting in increased thrombin production, decreased fibrinolysis, and activation of the complement pathway (Ahmadian *et al.* 2021). The imbalance of procoagulants and anticoagulants will stimulate endothelial cell damage and cell apoptosis. Fourth, dysregulation of the immune response triggered by T-cell lymphopenia, and inhibition of interferon signaling by the SARS-CoV 2 virus, overactivation of the body's natural immunity stimulates the activation of cytokines such as IL-6 and TNF- α . The worsening of the prognosis is associated with increased IL-6 and TNF- α (Ahmadian *et al.* 2021; Gagliardi *et al.* 2020, Gupta *et al.* 2020).

1.3 Kidney involvement in COVID-19

The main clinical manifestations of renal involvement in COVID-19 are proteinuria, hematuria, increased blood urea nitrogen (BUN) and creatinine, and decreased density on a computed tomography scan (CT scan) of the kidney (Cheng *et al.* 2020; Pei *et al.* 2020). Research shows that patients hospitalized due to COVID-19 with elevated serum creatinine levels have a higher severity of illness than patients with normal serum creatinine levels (Du *et al.* 2020). Another study conducted on a total of 139 patients, who were grouped into three groups, namely moderate, severe, and critical, showed that the ratio between BUN and creatinine levels could be an independent predictor of mortality in COVID-19 patients (Ok *et al.* 2021).

The kidney is one of the organs most affected by SARS-CoV-2 because the kidneys also express ACE2 receptors, even more than the lungs (Carriazo *et al.* 2020; Taheri *et al.* 2021). Kidneys play an important role in the body's endocrine function, the regulatory function of

blood vessels, acid-base balance, and as a means of transporting water and various solutes (Kasper *et al.* 2015). Recent human tissue RNA-seq data show that the expression of ACE2 in the kidney is almost 100-fold higher than in the respiratory organs (lungs). Therefore, kidney disease is very likely to be caused by a coronavirus that enters kidney cells through a pathway associated with the ACE2 receptor. Moreover, viral antigen immune complex formation or virus-induced specific immunological effector mechanisms (T lymphocytes or specific antibodies) can damage the kidneys (Du *et al.* 2020; Guzik *et al.* 2020).

1.4 *Creatinine and BUN levels correlations to COVID-19*

BUN and creatinine levels and the BUN/creatinine ratio are the main parameters that indicate kidney function). BUN and creatinine are end products of nitrogen metabolism in humans. By reason of that BUN and creatinine are small molecules, BUN and creatinine can be easily filtered from the nephrons of the kidney. Normally, about 30%–40% of BUN is reabsorbed from the tubules, whereas creatinine is not well reabsorbed. Multisystem inflammation, including cytokine storms, may occur in severe and critical cohorts of COVID-19 patients; it can increase BUN reabsorption and BUN/Creatinine ratio by a similar mechanism. Thus, this ratio will be useful in assessing the severity and survival of COVID-19 patients (Ok *et al.* 2021).

2 METHODS

This research uses an analytical observational research methodology with a cross-sectional approach. The subjects in this study were patients diagnosed with COVID-19 who were confirmed positive from the two times RT-PCR swab test at UNS Hospital and had an examination that included an examination of kidney function. Samples were collected from medical records. Data analysis using correlation test. The variables observed were creatinine and BUN levels in patients who were confirmed positive for COVID-19.

3 RESULTS

The results showed that 116 confirmed COVID-19 patients had their creatinine and BUN levels checked during treatment at the Sebelas Maret University Hospital in the period from January to August 2021. In collecting patient data, the mean creatinine was 2.47 (SD \pm 6.98) with levels of 73 mg/L being the largest value whereas 0.27 mg/L is the lowest. In addition, patient data collection also obtained a mean BUN of 25.87 (SD \pm 22.83) with a level of 116.28 mg/L being the largest value, and 0.00 mg/L being the lowest.

3.1 *Test of normality*

The normality test was interpreted through the Kolmogorov–Smirnov test because the number of samples was more than 50. In the data normality test results, the Sig value in the Kolmogorov–Smirnov test results table for the mortality parameter data, BUN, and creatinine $>$ 0.050. It can be concluded that the data is normally distributed.

3.2 *Creatinine chi-square test*

The Chi-Square Test correlation test was used because the data were normally distributed (Table 1). Interpretation of statistical test results obtained Asymptotic Significance (two-sided) of 0.020 and interpreted less than 0.05, p -value = 7,844 and it was interpreted as more than 5,991 (for $df = 2$, the significance value was 0.05) so that the research variables had a relationship. Based on statistical tests, it was found that there was a relationship between creatinine levels and the mortality rate of COVID-19 patients at UNS Hospital.

Table 1. The chi-square test correlation test.

Mortality Status	Creatinine		Asymp. Sig	Odds Ratio (OR)	Contingency Coefficient (C)	p-value
	High	Normal				
Survive	22	35	0.020	0.532	0.252	7.844
Not Survive	38	21				

The Contingency Coefficient (C) = 0.252 with a large effect of 25.2%, so the conclusion is that there is a 25.2% relationship between creatinine levels and the mortality rate of COVID-19 patients at UNS Hospital. Meanwhile, other factors that influence mortality but are not explained in this study are $100\% - 25.2\% = 74.8\%$.

The Odds Ratio (OR) is 0.532, which means that patients with increased creatinine levels are at risk of dying by 0.532 times greater than patients with normal creatinine levels.

3.3 Blood urea nitrogen chi-square test

Interpretation of statistical test results obtained asymptotic significance (two-sided) of 0.000 and interpreted less than 0.05, p-value = 19.673 and it was interpreted as more than 5.991 (for $df = 2$, the significance value was 0.05) so that the research variables had a relationship (Table 2). Based on statistical tests, it was found that there was a relationship between BUN levels and the mortality rate of COVID-19 patients at UNS Hospital.

Table 2. Blood urea nitrogen chi-square test.

Mortality Status	BUN		Asymp. Sig	Odds Ratio (OR)	Contingency Coefficient (C)	p-value
	High	Normal				
Survive	12	45	0.000	0.183	0.381	19.673
Not Survive	35	24				

The Contingency Coefficient (C) = 0.381 with a large effect of 38.1%, so the conclusion is that there is a 38.1% relationship between BUN levels and the mortality rate of COVID-19 patients at UNS Hospital. Meanwhile, other factors that influence mortality but are not explained in this study are $100\% - 38.1\% = 61.9\%$.

The Odds Ratio (OR) is 0.183, which means that patients with increased BUN levels are at risk of dying by 0.183 times greater than patients with normal BUN levels.

4 DISCUSSION

This study showed that there is a correlation between creatinine and BUN levels with mortality rates in COVID-19 patients. It is matched with several studies. A study conducted by (Xia *et al.* 2021) using Cox regression analysis showed that BUN and Creatinine were both significantly associated with COVID-19 disease progression (adjusted HR BUN 3.54, 95% CI 2.36-5.31, $P < 0.001$ and adjusted HR creatinine 2.84, 95% CI 1.92-4.21, $P < 0.001$) (Xia *et al.* 2021).

A study conducted on 138 hospitalized COVID-19 patients revealed an increase in creatinine and BUN of 15.5% and 14.1%, respectively. Another study revealed that mean Creatinine and BUN levels were 77 mol/L and 5.7 mmol/L, with increases in 14.4% and 13.1% of COVID-19 patients, respectively. Our findings showed that 7.1% and 4.4% of patients had an increase in Creatinine (mean level 64.1 mol/L) and BUN (4.37 mmol/L),

respectively. Studies by Xia *et al.* (2021) also found that BUN and creatinine are both risk factors for disease progression (Xia *et al.* 2021; Yan *et al.* 2021; Yang *et al.* 2020).

SARS-CoV-2 spreads mainly through the respiratory tract with symptoms of viral pneumonia as the first onset and the most characteristic symptoms. However, the level of ACE2 expression in the kidney, especially in the renal tubules, suggests that the kidney is another important target organ for the SARS-CoV-2 virus. This was also proven in the Middle-East Respiratory Syndrome Coronavirus (MERS-CoV) showing that SARS-CoV-2 can also attack directly renal tubular epithelial cells. SARS-CoV-2 was found isolated in the urine of patients. Viral particles were also detected in renal electron micrographs by autopsy, supporting the theory of direct viral attack in the kidney (Pan *et al.* 2020; Rabaan *et al.* 2020; Su *et al.* 2020).

The results of a study showed that patients with elevated BUN levels had a higher risk of increased mortality rates and the risk of worsening COVID-19 patients compared to normal BUN levels. This is because angiotensin-converting enzyme 2 (ACE2) is the main cellular receptor of SARS-CoV-2 and is highly expressed in renal epithelial cells. This is because the viral infection can directly cause the interaction of SARS-CoV-2 with receptors in the kidney to reduce ACE2 expression, resulting in abnormal activation of the renin-angiotensin-aldosterone system (RAAS). Activated RAAS can significantly increase water absorption by the renal tubules by increasing urea resorption, which leads to an increase in BUN levels. Elevated BUN levels are not only an indicator of renal dysfunction but may also reflect inflammatory status, catabolism, nitrogen balance, and renal hypoperfusion due to hypovolemia, sepsis, or decreased cardiac output, many of which have also been reported to be the cause of worsening outcomes in COVID-19 patients. Coagulation status can progress and worsen along with systematic inflammatory resuscitation of the pons and multiple organ injury (Liu *et al.* 2021).

In a cohort study by Ok *et al.* (2021), creatinine counts were similar in severe and non-severe patients. The BUN/creatinine ratio was higher in the severe patient group and was strongly correlated with disease severity ($\rho = -0.810$). In the adjusted multivariate logistic and Cox regression models, the BUN/Creatinine ratio was an independent predictor of disease severity (OR = 1.70) and mortality (HR = 1.02). Finally, the study findings suggest that an increase in the BUN/creatinine ratio is an independent predictor of COVID-19 disease severity and survival. The BUN/Creatinine ratio can provide important prospective information in the evaluation of COVID-19 patients on admission (Ok *et al.* 2021).

5 CONCLUSION

Finally, it can be concluded that there is a relationship between creatinine and BUN levels with mortality rates in patients with COVID-19 at Sebelas Maret University Hospital.

ACKNOWLEDGEMENT

This paper and the research behind it would not have been possible without the exceptional support of my outstanding lecturers, dr. Berty, and dr. Evi, from the Department of Internal Medicine, UNS Hospital, and dr. Sigit from the Faculty of Medicine UNS. Their enthusiasm, knowledge, and exacting attention to detail have been an inspiration and kept my work on track from my first encounter with this paper. We also would like to thank the Department of Research UNS Hospital for giving us permission to be able to do our research.

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Dementia prevalence and distribution in Central Java (Neuroscience)

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ABSTRACT: Impaired cognitive function is a global public health problem that occurs around the world associated with old age. It is characterized by various degenerative diseases such as Dementia and Alzheimer's whose numbers are increasing every year. Dementia is not a specific disease but is rather a general term for the impaired ability to remember, think, or make decisions that interfere with doing everyday activities. Alzheimer's disease is the most common type of dementia. Though dementia mostly affects older adults, it is not a part of normal aging. People with dementia have symptoms of cognitive decline that interfere with daily life—including disruptions in language, memory, attention, recognition, problem-solving, and decision-making. The global burden of dementia has been estimated that 35,6 million people are living with dementia worldwide and projected to increase to 65,7 million by 2030 and 115.4 million by 2050. In Indonesia, the dementia prevalence increased twice every 5 years after passing the age of 60 years and reached sixth place among nine countries in Asia. A dementia study based on SurveyMETER that was held in December 2015, revealed that the dementia prevalence in DIY and Central Java was 20.1%, which is more higher than the global condition that under 10%.

1 INTRODUCTION

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative disorders. It causes memory loss, cognitive impairments, and a decline in the ability to perform daily tasks. The most prevalent underlying pathologies of dementia are AD, vascular dementia (VaD), dementia with Lewy bodies, and frontotemporal dementia. The available data revealed that AD accounted for approximately 60% of dementia cases and VaD for 20% (Cao *et al.* 2020). It is difficult to distinguish between AD and VaD because of their symptomatology, pathophysiology, and risk factors over-lap (Kalaria *et al.* 2008; Wolters & Ikram 2019). Each pathology contributes to varying degrees, resulting in a spectrum of patients, with pure cerebrovascular disease and pure AD representing the extremes (Erkinjuntti 2001; Wolters & Ikram 2019).

AD is characterized by a progressive cognitive decline that typically begins with an impairment in the ability to form recent memories, but ultimately affects all intellectual functions, resulting in total dependence on basic daily functions and early death. AD is characterized by diffuse and neurotic extracellular amyloid plaques and intracellular neurofibrillary tangles, as well as reactive microgliosis, dystrophic neurites, and the loss of neurons and synapses (Serrano-Pozo *et al.* 2011). Although these pathological lesions do not fully explain the clinical manifestations of the disease, it has been hypothesized that changes in the production and processing of amyloidprotein may be the primary initiating factor. Age,

genetics, and nongenetic antecedent factors, as well as advancing age, are believed to play significant roles in the underlying causes of these multifaceted changes (Mayeux & Stern 2012).

In this chapter, we will discuss the prevalence and incidence rates of AD globally, specifically in Central Java.

2 RESULTS

2.1 Global epidemiology

The global burden of dementia has been estimated that 35,6 million people are living with dementia worldwide and projected to increase to 65,7 million by 2030 and 115.4 million by 2050 (Prince *et al.* 2013). Due to the rapid aging of both developed and developing nations, the frequency is expected to double every 20 years until 2040. The magnitude of the impending increase due to the aging of the population is substantial and will be a costly public health burden in the future (Mayeux & Stern 2012).

The prevalence of AD likewise increases exponentially with age, rising significantly beyond age 65. Between the ages of 60 and 85, the frequency of dementia, or AD, has increased nearly 15-fold (Evans *et al.* 1989). Compared to Africa, Asia, and Europe, the prevalence of AD appears to be significantly higher in the United States, which may be a result of different methods of detection. For unknown reasons, the frequency may be higher among African-American and Hispanic populations living in the United States, but lower among Africans in their home countries (Hendrie *et al.* 2001).

Based on studies conducted in Boston, Framingham, Rochester, and Baltimore, Brookmeyer *et al.* approximated the age-specific AD incidence rates doubled every 5 years after age 60 and increased from approximately 0.17% per year at age 65 to 0.71, 1.0, and 2.92% per year at ages 75, 80, and 85, respectively (Brookmeyer *et al.* 1998). This finding is consistent with the vast majority of research that has assessed the age-specific incidence of AD by gender and ethnicity (Prince *et al.* 2013).

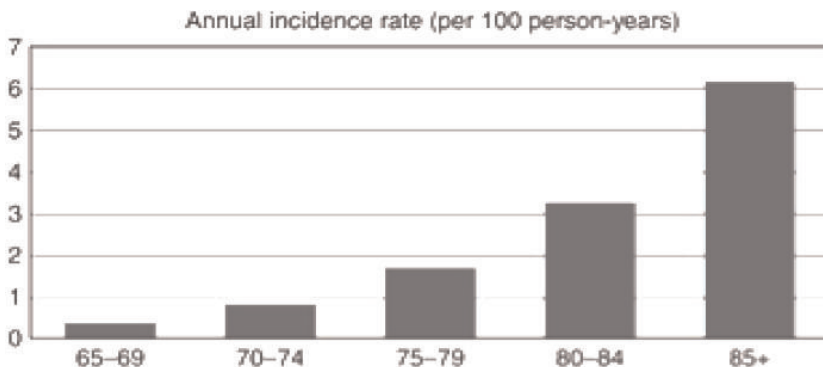


Figure 1. The annual incidence rate (per 100 person-years) for AD (Mayeux & Stern 2012).

Numerous factors have been linked to an increased risk of AD, but cerebrovascular illness and its precursors are the most frequently cited (Table 1). Risk is increased by a history of diabetes, hypertension, smoking, obesity, and dyslipidemia. Intriguingly, cerebrovascular diseases, such as large cortical infarcts, strategically placed single infarcts, multiple small infarcts, cerebral hemorrhage, hypo-perfused cortical changes, white matter changes, and vasculopathies, are all precursors to dementia in general (Mayeux & Stern 2012).

Table 1. Factors that modify the risk of AD (Mayeux & Stern 2012).

Risk factor	Direction	Possible mechanism
Cardiovascular disease	Increased	Parenchymal destruction Strategic location \uparrow $A\beta$ deposition
Smoking	Increased	Cerebrovascular effects Oxidative stress
Hypertension	Increased and decreased	Microvascular disease
Type II diabetes	Increased	Cerebrovascular effect Insulin and $A\beta$ compete for clearance
Obesity	Increased	Increased risk of type II diabetes inflammatory
Traumatic head injury	Increased	\uparrow $A\beta$ and amyloid precursor protein deposition
Education	Decreased	Provides cognitive reserve
Leisure activity	Decreased	Improves lipid metabolism, mental stimulation
Mediterranean diet	Decreased	Antioxidant, anti-inflammatory
Physical activity	Decreased	Activates brain plasticity, promotes brain vascularization

2.2 Central Java epidemiology

Asia has the biggest number of dementia patients, about 22.9 million, as compared to both Europe (10.5 million) and the United States (9.4 million). According to data published by AD International, the prevalence of dementia in Asia will continue to rise. In 2015, it is estimated that one million Indonesians will be afflicted with dementia, a number that will rise to about two million by 2030 and nearly four million by 2050 (Prince *et al.* 2015).

In Indonesia, there is a long-standing misconception among family members regarding dementia. Many family members and members of the general public viewed memory loss and cognitive impairment as a normal part of the aging process (Glueckauf *et al.* 2005). The average time between patients' memory complaints and their first dementia-related hospitalization was 7.1 years (3.7 years). The majority of dementia patients (56.2%) did not receive outpatient care prior to their memory disorder (Luzny *et al.* 2014). In a survey of adults aged >20 , 45.6% of respondents did not consider dementia to be a disease, and 46.0% believed dementia was caused by multiple factors (Yong *et al.* 2015). This lack of awareness of dementia symptoms among caregivers poses a significant obstacle to detecting this debilitating illness. In addition to understanding risk factors, the elderly and their caregivers need to be aware of the earliest dementia symptoms.

In Indonesia, the prevalence of dementia increased twice every 5 years after passing the age of 60 years and reached sixth place among nine countries in Asia. A dementia study based on SurveyMETER held in December 2015, revealed that the dementia prevalence in DIY and Central Java was 20.1%, with most of the subjects being less educated and residing in rural areas (Suriastini *et al.* 2020).

In Central Java, the prevalence of dementia was higher among female subjects. In addition to a longer lifespan, hormonal changes may be a contributing factor. The rapid decline in estrogen levels may play a significant role. The risk factors for dementia in both sexes were advanced age, a low level of education, rural or remote living, a history of stroke, and unemployment (Suriastini *et al.* 2020). This is also consistent with previous research (Luzny *et al.* 2014; Prince *et al.* 2013; Yong *et al.* 2015).

The increasing prevalence was also linked to a lack of caregiver awareness of early dementia symptoms. Less than 12% of caregivers could identify memory loss as a dementia symptom (Suriastini *et al.* 2020). The general population's level of knowledge and comprehension of dementia has been revealed by studies conducted in other nations with similar

findings (Organization & Organization 2020). By seeking medical consultation, caregivers who have a greater understanding of the early symptoms of dementia contribute to an early diagnosis. By detecting early signs, they can provide early warning to family members and healthcare professionals. The knowledge of the carers is also essential when making decisions on the care of the elderly (Garvey *et al.* 2011). A study by Chodos *et al.* revealed a positive correlation between the knowledge of carers and the amount of compliance that promotes the quality of care for the elderly (Chodos *et al.* 2007). Knowledge and awareness are essential for family members to notice signs and seek medical help (Khonje *et al.* 2015).

3 CONCLUSIONS

The prevalence of dementia was elevated in Central Java and DIY. Age, lack of education, a history of stroke, and unemployment were risk factors. This was also attributed to caregivers' lack of awareness of AD's early symptoms. The prevalence data and level of knowledge about AD should provide evidence-based information to all parties and be clear enough to initiate an evaluation to increase awareness of symptoms, including early prevention and treatment of AD. Further research needs to be conducted to know AD prevention and treatment.

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Effect of N-Acetylcysteine on superoxide dismutase serum level and mucociliary transport time in chronic suppurative otitis media

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ABSTRACT: Chronic suppurative otitis media (CSOM) is an inflammation and infection of the middle ear. Eustachian tube mucociliary transport is chief for the removal of the middle ear inflammation products allowing recovery of the affected middle ear mucosa, local circulation, and renewal of normal air pressure in the middle ear. N-Acetylcysteine (NAC) is an antioxidant agent that is highly effective despite its limited reactive oxygen species (ROS) activity. It can also reduce mucosal secretion and improve mucociliary transport in CSOM. To analyze the effect of NAC on SOD supplementation of SOD serum level and mucociliary transport in CSOM patients. This research was conducted with the pre-posttest control group design. Thirty adult patients with CSOM were separated into control and study groups. Both groups were given antibiotics based on culture examination and fifteen patients in the study group were given NAC 600 mg/day. Pre- and post-treatment with NAC, the SOD serum levels, and mucociliary transport time were compared. The mean serum level of SOD increased significantly after the intervention with NAC in the study group, compared to the control group ($p < 0.05$). There was also a significant difference in mucociliary transport time in the study group compared to the control group ($p = 0.01$). As an antioxidant, NAC has been shown to increase SOD serum level and improve mucociliary transport time in the CSOM. Higher levels of SOD serum with improved mucociliary transport time are correlated with faster healing rates, therefore, the administration of NAC in patients with CSOM is highly recommended.

1 INTRODUCTION

Chronic suppurative otitis media (CSOM) is an inflammation and infection of the middle ear characterized by persistent drainage from the middle ear associated with a perforated ear drum. CSOM is a disease that develops in tropical countries and affects about 330 million patients worldwide (Poluan *et al.* 2021).

Eustachian tube dysfunction is also widely recognized as the most important pathogenesis factor. One of the functions of the eustachian tube is to remove secretions from the middle ear space in the nasopharynx through mucociliary transport (Faazah *et al.* 2021). Therefore, measuring the length of time required for ciliary transport could help in estimating the pathogenic changes to the mucosal membrane.

Reactive oxygen species (ROS) are key signaling molecules that play an important role in the progression of an inflammatory disorder. An enhanced ROS generation by polymorphonuclear neutrophils (PMNs) at the site of inflammation causes endothelial dysfunction and tissue injury (Mittal *et al.* 2015). Superoxide dismutase (SOD) is an enzyme that is important in the detoxification of superoxide radicals because they are the first substances produced in the majority of reactions that gave rise to organic free radicals (Anggraeni *et al.* 2014).

Although NAC is not an antibiotic, it possesses antimicrobial properties and breaks down bacterial biofilms of medically relevant pathogens (Garça *et al.* 2013).

A study on the effect of NAC on serum SOD levels has already been conducted in patients with schizophrenia, but research specifically in CSOM patients has never been reported. Research by Camellia *et al.* found that the administration of NAC as an adjuvant therapy along with risperidone had a significant effect on serum SOD levels compared to the control group (Camellia *et al.* 2021). Sari *et al.* found no significant difference in mucociliary transport time in CSOM patients without cholesteatoma after 1 week of NAC administration. In this study, along with the measurement of SOD serum level after 2 weeks of treatment, we also assess the mucociliary function of the middle ear in CSOM patients. This research aimed to determine the effect of NAC treatment on the serum level of SOD and mucociliary transport time in CSOM patients.

2 METHODS

We conducted a clinical trial with a non-randomized pre- or post-test control group research design to investigate the efficacy of NAC as adjuvant therapy in CSOM. The research consists of 30 CSOM adult patients who were separated into two groups. Both groups were given antibiotics based on culture examination and in the study group patients were given NAC supplementation of 200 mg 3 times a day (600 mg/d) for 2 weeks. Efficacy was determined by comparing SOD and mucociliary transport time pre- and post-treatment. The study was conducted at the ENT clinic of Dr. Moewardi Hospital Surakarta from June to August, 2022. Subjects were included if they had CSOM without cholesteatoma with otorrhea at least within 3 months and were willing to participate as indicated by informed consent. Meanwhile, the exclusion criteria were CSOM patients who have received topical antibiotic ear drops for the last 7 days, patients with systemic diseases, patients who are immunocompromised and were taking immunosuppressant medicines, patients with congenital abnormalities of the ear, patients with external ear infections, and CSOM patients with complications. The study was approved by the research Ethics Committee at the Faculty of Medicine, Universitas Sebelas Maret, Surakarta, Indonesia.

2.1 SOD measurement

The measurement of SOD serum level was performed on blood samples using the SOD Human ELISA kit BIOENZY, USA. The ELISA procedures were conducted in the Biomedical Laboratory Faculty of Medicine, Universitas Sebelas Maret.

2.2 Mucociliary transport time measurement

The mucociliary transport time is measured by instilling 0.1 mL of ciprofloxacin ear drops into the ear cavity. The time taken by the patient for bitterness in the pharynx will be recorded in minutes and seconds.

2.3 Statistical analysis

Data were collected and analyzed using the SPSS software version 26.0 (USA). Serum level of SOD and mucociliary transport time in both groups were compared using the independent T-test. A paired t-test was conducted to compare the mean of SOD serum level and mucociliary transport time before and after treatment. Furthermore, an ANCOVA test was also conducted to compare the changes in SOD serum level and mucociliary transport time after treatment.

3 RESULTS AND DISCUSSION

The average age of the NAC and control groups were 32.67 ± 4.67 and 31.53 ± 3.78 years, respectively. The average duration of illness was 5.17 ± 1.55 months and the average BMI

was $22.1 \pm 3.91 \text{ kg/m}^2$. There were more female subjects than male, more patients with mild hearing loss than those with moderate hearing loss, and slightly more subjects with unilateral hearing loss compared to those with bilateral hearing loss in both groups.

Table 1. Demographic characteristics of CSOM patients.

Parameters	Control (n = 15)	NAC (n = 15)	<i>p</i>
Age	32.67 ± 4.67	31.53 ± 3.78	0.47
Sex			0.50
Male	6 (40%)	7 (46.67%)	
Female	9 (60%)	8 (53.33%)	
Smoking			0.50
Yes	6 (40%)	7 (46.7%)	
No			
BMI	21.93 ± 3.81	22.27 ± 4.15	0.82
Duration (months)	5.27 ± 1.75	5.07 ± 1.39	0.73
Degree of hearing loss mild			0.23
moderate	7 (46.67%)	10 (66.67%)	
	8 (53.33%)	5 (33.33%)	
Affected ear			0.35
unilateral	8 (53.33%)	6 (40%)	
bilateral	7 (46.67%)	9 (60%)	

Before the treatment, both groups had their SOD serum levels measurement and there was no significant difference in baseline serum levels of SOD. The comparison of SOD serum levels before treatment is presented in Table 2.

Table 2. Independent t-test before therapy.

Variable	Control	NAC	<i>P</i>
SOD	25.84 ± 33.45	24.37 ± 28.64	0.89

After 2 weeks of treatment, there was a statistically significant increase in the levels of serum SOD post-treatment ($p < 0.05$). The difference in SOD serum levels treatment was then compared (Table 3).

Table 3. SOD levels pre- or post-treatment.

Group	SOD Pre	SOD Post	Δ	<i>p</i>	Ancova <i>p</i> value
Control	25.84 ± 33.45	24.62 ± 32.87	1.22	0.32	0.001
NAC	24.37 ± 28.64	175.47 ± 114.60	151	0.00	

Changes in SOD serum level in the control group and NAC group were $1.22 \pm 4.66 \text{ U/mL}$ and $151.10 \pm 103.45 \text{ U/mL}$ respectively which showed a significant difference between the groups ($p < 0.05$). In this study, 11 samples (36.67%) from both groups tasted bitter after the instillation of ear drops and the remaining 19 samples (63.33%) did not taste bitter. Patients who had a bitter taste were then examined for the mucociliary transport time. The changes in mucociliary transport time are presented in Table 4.

Table 4. Mucociliary transport time.

Group	n	Time Pre	Time Post	Δ	<i>p</i>	Ancova <i>p</i> value
NAC	7	33.56 ± 2.73	17.13 ± 1.20	16.42	0.01	0.001
Control	4	34.22 ± 3.01	33.67 ± 3.50	0.55	0.372	

There was a significant difference in the mucociliary transport time between groups. The changes in mucociliary transport time in the NAC group were found to be 16.42 ± 7.02 minutes and in the control group, it was 0.55 ± 0.84 minutes.

4 DISCUSSION

CSOM has been described as a multifactorial disease. Many factors are responsible for the chronicity of inflammation in otitis media such as genetics, eustachian tube malfunction, auto-immunity, infection, osteoclastic activity, cytokines, endotoxins, and lipid peroxidation products related to oxidative stress. All these factors also increase the oxygen free radicals (FORs) which are necessary for metabolic and immunological responses. The body's defense cells, including neutrophils, monocytes, and macrophages, create FORS by combatting antigens. However, excessive production of FOR may damage the tissues and lengthen the duration of inflammation. Antioxidants are substances that prevent the damage that FORs do to cells and maintain a healthy level of oxidative equilibrium (Garça *et al.* 2015).

The results of this study indicated that NAC can significantly increase SOD serum levels. It is in line with the results of research by Camellia, who also reported that NAC may increase SOD serum levels (Camellia *et al.* 2021). N-acetylcysteine is a thiol, a key precursor of cellular glutathione (GSH) synthesis, which easily penetrates cell membranes and induces detoxification, and acts directly to reduce free radicals. Glutathione is one of the body's most important antioxidant compounds that help neutralize free radicals that can damage cells and tissues (Özcan *et al.* 2018). N-acetylcysteine as an indirect antioxidant via an increase in the intracellular tripeptide containing cysteine (L- γ -glutamyl-L-cysteinyl-glycine), better known as GSH and NAC as a potent antioxidant is directly linked to its ability to increase levels of intracellular cysteine with subsequent increase in GSH (Tenório *et al.* 2021).

NAC rapidly decreases the viscosity of mucus in order to improve mucociliary transport and has been shown to decrease bacterial biofilm formation (Goetz *et al.* 2022). Superoxide dismutase, which decreases during inflammatory processes such as CSOM due to increased levels of free radicals, eventually increases due to the free radical-reducing effects of NAC (Kopincova *et al.* 2019).

Antioxidants such as SOD are substances that inhibit the oxidation process by capturing and stabilizing free radicals. Antioxidants cause reactions to convert oxidants into harmless forms and inhibit the formation of new free radicals. To protect against these toxic products, the body produces an enzymatic antioxidant system such as SOD. When oxidants are increased as a result of chronic inflammatory processes, the antioxidant system is activated to eliminate them (Anggraeni *et al.* 2014).

In addition to SOD, the NAC group also had a shorter mucociliary transport time than the control group. This is consistent with the research by Sari *et al.* who also pointed out that NAC can reduce mucociliary transport time (Sari *et al.* 2015). Eustachian tube mucociliary transport is very important to reduce the inflammatory process in the middle ear, which can affect the healing of the middle ear mucosa, local circulation, and an improvement of middle ear pressure (Sagiroglu *et al.* 2019).

NAC may reduce bacterial adhesion to epithelial cells and has antibacterial properties that may damage biofilms produced by *P.aeruginosa* (Sari *et al.* 2015). Endotoxins or biofilms of bacteria and proteolytic enzymes produced by neutrophils that appear in CSOM are thought to reduce cilia activity and frequency of cilia movement (Garça *et al.* 2013; Zein *et al.* 2015).

5 CONCLUSION

N-acetylcysteine has an antioxidant effect, which may increase SOD serum levels and decrease mucociliary transport time. Higher SOD levels with lower mucociliary transport time correlate with faster healing rates. This study has several shortcomings. First, the number of subjects in both groups is relatively small. Second, both samples in the study were not randomly selected. For future research, it is recommended to increase the number of research subjects and randomize the sample to minimize bias.

ACKNOWLEDGMENTS

The authors affirm no conflict of interest in this study.

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Effects of toxoplasma gondii infection on malondialdehyde and C-reactive protein levels in pregnant rats

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ABSTRACT: Toxoplasmosis is a human disease due to intracellular infection of *Toxoplasma gondii*, which induces oxidative stress and inflammation. These defense mechanisms often result in massive cell damage, which is characterized by increases of malondialdehyde (MDA) and proinflammatory cytokine productions. Interleukin-6 as an example of proinflammatory cytokine stimulates the hepatocytes to release a soluble mediator of the innate immune system, C-reactive protein (CRP), in order to inhibit the parasite infection. The purpose of this study was to investigate the effects of *T. gondii* infection on serum MDA and CRP levels in pregnant rats. **Materials and Methods:** This laboratory experiment with post-test only group design used 16 female Wistar rats (*Rattus norvegicus*) aged 6–8 weeks and weighing 200–250 g. Selected female rats were randomly divided into four groups: A control group which was not exposed to any toxoplasma isolates, and the other three groups which were differentiated based on the dose of toxoplasma RH strain isolate given (101 tachyzoites, 102 tachyzoites, and 103 tachyzoites respectively). On Day 12 of pregnancy, all rats in the treatment groups were intraperitoneally injected with 2 ml of *Toxoplasma* isolates. Blood samples were then collected in the end of pregnancy for measurement of serum MDA and CRP levels. **Results:** Serum MDA and CRP levels increased significantly in all pregnant rats of T groups, compared to those of control group ($p < 0.001$). Furthermore, serum MDA and CRP levels in all four groups were dose dependent manner. Sequentially from the control group to the third treatment group, mean difference in MDA levels was (1.68 ± 0.239 nmol/ml; 5.375 ± 0.234 nmol/ml; 8.737 ± 0.214 nmol/ml; and 10.8 ± 0.597 nmol/ml) and in CRP levels was (2.975 ± 0.227 mg/L; 4.382 ± 0.214 mg/L; 15.727 ± 0.537 mg/L; and 17.970 ± 0.09 mg/L). **Conclusion:** *Toxoplasma* infection increased serum MDA and CRP levels in dose dependent manner in pregnant rats.

1 INTRODUCTION

Toxoplasmosis is a systemic protozoan disease caused by *Toxoplasma gondii* (Halonen, Sandra K & Weiss 2013), which can attack warm-blooded animals including humans. It is the most common infection in humans and warm-blooded animals and spreads throughout the world (Yulianti 2015). Toxoplasmosis occurs in every country with seropositivity rates from 10% to 90% (Torgerson & Mastroiacovo 2013). The incidence of congenital toxoplasmosis depends on gestational age in the

absence of prior immunity and the degree of exposure to toxoplasmosis during pregnancy. For untreated women, transmission rates are 25% in the first trimester, 54% in the second trimester, and 65% in the third trimester (Torgerson & Mastroiacovo 2013) respectively.

Transmission of toxoplasmosis generally occurs through ingestion of cysts in the tissue, ingestion of oocysts from contaminated food or water, and the intestine is the main site of *Toxoplasma gondii* infection after the cyst is ingested orally (McAuley 2014). Transmission of toxoplasmosis infection from mother to fetus (congenital toxoplasmosis) can occur in seronegative mothers where tachyzoites present in the blood can cross the placenta and infect the fetus.

The body's immune response to *T. gondii* infection requires an innate immune response and an acquired immune response that involves a series of cellular interactions such as parasites, enterocytes, monocytes, dendritic cells, macrophages, NK cells and neutrophils (Halonen, Sandra K & Weiss 2013). *T. gondii* infection causes oxidative stress which causes an imbalance between the free radical-producing system and the cellular defense system, namely an increase in the production of free radicals or a decrease in antioxidant defense activity or both (Sasai *et al.* 2018). C-Reactive Protein (CRP) is an important component of the non-specific immune response, which is increased during infection and inflammation (Dincel & Atmaca 2016). MDA is a significant biomarker that can be used to measure oxidative stress (Sproston & Ashworth 2018). Therefore, researchers are encouraged to examine the relationship between CRP and MDA levels in pregnant rats with a toxoplasmosis model.

2 METHODS

This research used a laboratory experimental study using a Randomized Control Trial (RCT) with a posttest only research design and with a control group design. Treatment of pregnant female rats, blood sampling, and examination of MDA and CRP levels were conducted at the Central Laboratory of Food and Nutrition Studies (PAU) Gadjah Mada University of Yogyakarta. The research subjects were female rats aged 6–8 weeks, weighing 200–250 grams, being healthy, having shining eyes, not having dull fur, being active, and having good appetite. Rats were given standard BR II food while drinking was given freely (at libitum), and the cage environment was homogeneous. Exclusion criteria were rats that gave birth and rats that died during the treatment period. The isolates of *T. gondii* used with the RH strain were taken from the Center for Veterinary Research (BBALITVET) Bogor. In this study, it was found ethically appropriate and declared ethically feasible pursuant to Statement Letter, No. 56/UN27.06.6.1/KEP/EC/2021 issued by Universitas Sebelas Maret.

In this study, the normal control group consisted of 4 normal pregnant rats, and the treatment group included 4 rats with a dose of 101 tachyzoites, 102 tachyzoites, and 103 tachyzoites. Each rat was first adapted to laboratory conditions for 1 week. At this stage, the rats were fed with standard pellet BR-2 and water from PAM ad libitum. Female rats are mated with mono-mating, that is, one female was mated with one male. The diagnosis of pregnancy was obtained after 17 hours of mating and evaluated for the presence of a copulatory plug, which is a plug that covers the rat's vagina from the cervix to the vulva as an indicator of pregnancy. Pregnancy is indicated by a copulatory plug.

Toxoplasma isolate was administered intraperitoneally as much as 2 ml on Day 12 of pregnancy (Dubey *et al.* 1997). Then levels of CRP and MDA were measured through rat blood samples on Day 17 of pregnancy. Mice were tested positive for toxoplasmosis if they showed symptoms of ascites, their hair stood on end, they were lazy to move, and they tended to be in groups.

MDA and CRP levels were analyzed by one-way ANOVA test, which was followed by a post-hoc Tukey LSD test with a 95% confidence degree ($\alpha = 0.05$). The data were analyzed with the SPSS 21 software for Windows.

3 RESULTS

The subjects in this study were sixteen female rats that had gone through the process of pregnancy and induction with toxoplasma isolates on Day 12 of pregnancy. Subjects in this study were divided into four groups with the same number for each group. Each group, apart from the control group, was then given toxoplasma induction with different doses. Determination of the

rats that were put into each group was done randomly. TG1, TG 2, and TG3 showed the toxoplasma isolates with doses of 10^1 tachyzoites, 10^2 tachyzoites, and 10^3 tachyzoites respectively.

Based on the normality test, the variables CRP and MDA in each group had the p-value of > 0.05 , meaning that data were normally distributed.

Table 1. Results of one-way ANOVA test data on MDA and CRP values of rats after toxoplasma induction.

	Mean \pm SD				p-value
	CG	TG1	TG2	TG3	
MDA (nmol/mL)	1.68 \pm 0.239	5.37 \pm 0.234	8.73 \pm 0.214	10.8 \pm 0.597	$< 0.001^{**}$
CRP (ng/mL)	2.97 \pm 0.227	4.38 \pm 0.214	15.73 \pm 0.537	17.97 \pm 0.09	$< 0.001^{**}$

Notes

*significant $\alpha = 0.05$

**significant $\alpha = 0.001$

The data in Table 1 show that there were significant differences in the levels of MDA ($p < 0.001$) and CRP ($p < 0.001$) in the four groups. The data mean difference in the levels of MDA and CRP in the four groups showed an increase in accordance with the increase in the dose of toxoplasma tachyzoite injected into rats.

Table 2. Results of Tukey's post-hoc analysis of mice MDA and CRP values after toxoplasma induction.

Treatment group	Mean difference and p-value MDA (nmol/mL)			
	CG	TG 1	TG2	TG3
CG		3.69(<0.001) **	7.05(<0.001) **	9.12 (<0.001) **
TG 1			3.36(<0.001) **	5.42(<0.001) **
TG 2				2.06(<0.001) **

Treatment group	Mean difference and p-value CRP (ng/mL)			
	CG	TG 1	TG2	TG3
CG		1.40(<0.001) **	12.75(<0.001) **	14.99 (<0.001) **
G 1			11.34(<0.001) **	13.58(<0.001) **
TG 2				2.24(<0.001) **

Notes

* significant $\alpha = 0.05$

** significant $\alpha = 0.001$

4 DISCUSSION

Tukey's post-hoc test conducted on both variables showed that each group had a significant difference ($p < 0.001$) against the other groups. Meanwhile, when viewed from the resulting mean difference, the larger the dose of toxoplasma isolate given, it would lead to a greater increase in MDA and CRP levels in pregnant rats of the Toxoplasma model.

MDA is the final product produced by the degradation of cell membrane phospholipids during the lipid peroxidation process (Singh *et al.* 2014). MDA is also used as a marker of oxidative stress and lipid peroxidation. Recent studies published by Dincel and Atmaca confirmed that oxidative stress and

reduction of endogenous antioxidant capacity that occur in acute toxoplasmosis are associated with high MDA levels (Lorente *et al.* 2015). The high concentration of MDA is due to the increased of production free radicals that lead to more lipid peroxidation and then higher oxidative damages in cellular membranes (Sulaiman & Noori 2022). The result of this study is consistent with it, where the Toxoplasma isolate with a dose of 103 tachyzoites showed higher MDA levels (10.8 ± 0.597 nmol/ml) than the control group (1.68 ± 0.239 nmol/ml) and the two groups. others with lower isolate doses.

C-Reactive Protein (CRP) is an important component of the non-specific immune response, which increases during infection and inflammation. CRP is synthesized mainly in hepatocytes, but also in smooth muscle, macrophages, endothelial cells, lymphocytes and adipocytes (Dincel & Atmaca 2016). This study found a significant difference in CRP levels in pregnant rats induced with toxoplasma isolate ($p < 0.001$). The increase in CRP levels was also seen from the absolute value obtained in the mean difference in each group, where the higher the dose of toxoplasma isolate given, it was directly proportional to the increase in CRP levels. Several studies related to the relationship between CRP levels with toxoplasma infection showed different results. Birgisdóttir *et al.* in their study found a weak ($r = 0.07$) but statistically significant ($p = 0.02$) association between elevated CRP and toxoplasma infection in patients with asthmatic symptoms (Sproston & Ashworth 2018). This may be related to the inflammation that occurs at the time of toxoplasma infection, where CRP shows increased expression during inflammation (Birgisdóttir *et al.* 2006). The result of this research is related to that of Egorov *et al.* that Ig G seropositivity (a marker of latent infection) was significantly associated with elevated inflammation biomarker VCAM-1, ICAM-1 and CRP. There were four biomarkers linked to *T. gondii* in previous in vivo or in vitro studies and known as predictors of adverse health outcomes in humans: Soluble intercellular adhesion molecule 1 (ICAM-1), soluble vascular cell adhesion molecule 1 (VCAM-1), C-reactive protein (CRP), and serum amyloid A (SAA) (Egorov *et al.* 2021).

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Humoral immune response and cellular immune response of CoronaVac vaccine following COVID-19 vaccination

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ABSTRACT: Inactivated coronavirus disease (COVID-19) vaccine, CoronaVac (Sinovac Biotech) has constraints in stimulating cellular immune response compared to humoral immune response leading to the inability to produce antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which plays role in providing neutralization and protection from SARS-CoV-2. Humoral and cellular immune responses can be evaluated by examining CD4⁺ and CD8⁺ percentages, respectively. This study analyzed the potentiality of the inactivated COVID-19 vaccine in inducing humoral and cellular immune responses by evaluating its correlation with the SARS-CoV-2 antibody. A cross-sectional study was performed on 50 healthcare workers who met our inclusion criteria. The CD4⁺ and CD8⁺ T cells were examined with BD FACSCanto™ II using flow cytometry. ROCHE Cobas® E411 with electrochemiluminescence immunoassay (ECLIA) was employed for examining the SARS-CoV-2 antibody. Spearman correlation test was used for analyzing the data statistically and the significance was determined with p value less than 0.05. This study obtained the mean values of CD4⁺ percentages, CD8⁺ percentages and SARS-CoV-2 antibody were $32.98 \pm 7.74\%$, $27.72 \pm 8.58\%$, and 87.18 ± 142.95 U/ml, respectively. The correlation test yielded a statistically significant positive weak correlation of CD4⁺ with SARS-CoV-2 antibody ($r = 0.322$ $p = 0.023$) and a significant negative weak correlation of CD8⁺ with SARS-CoV-2 antibody ($r = -0.297$ $p = 0.036$). To sum up, there are positive correlation of CD4⁺ percentage and a negative correlation of CD8⁺ percentage with SARS-CoV-2 antibody. This evidences that the inactivated COVID-19 vaccine can produce a humoral immune response. However, the finding of negative correlation indicates that the ability of this vaccine to induce cellular immune response has not been able to be proven.

1 INTRODUCTION

The coronavirus disease (COVID-19) global pandemic that hit Indonesia forced the government to think about the best strategy to deal with the COVID-19 pandemic. A definitive treatment for the COVID-19 pandemic has yet to be found, and this is in line with the knowledge that finding a treatment for a viral infection is far more complicated than finding a treatment for a bacterial infection (Dhama *et al.* 2020). Severe acute respiratory syndrome CoV-2 (SARS-CoV-2) inactivated vaccine China's CoronaVac (Sinovac Biotech Ltd., Beijing, China) vaccination in healthy individuals generates immune protection against COVID-19. Prevention of COVID-19 infection by using vaccination as a mode of passive immunity is a solution to reduce the incidence of COVID-19 infection and further reduce the severity of COVID-19 infection (Sadarangani *et al.* 2021).

In addressing COVID-19, a country's ability is highly dependent on the ability of health facilities, including healthcare workers, to cope with the complications of the COVID-19 pandemic. As the front-liners in dealing with the COVID-19 pandemic, healthcare workers are expected to have adequate immunity against COVID-19 infection. The Indonesian Government has made healthcare workers mandatory for the primary and priority target of the COVID-19 vaccination program. Indonesia uses inactivated CoronaVac (Sinovac Biotech Ltd.) vaccine for COVID-19 vaccination. Healthcare workers must receive two doses (primary dose) of inactivated vaccine in facing the COVID-19 pandemic (Mahendradhata *et al.* 2021).

Despite receiving COVID-19 vaccination, many healthcare workers are still reinfected with COVID-19 infection (Nisha *et al.* 2022). Many questions arise about the ability of inactivated vaccines to trigger an immune response, which is the primary objective of vaccination. An inactivated vaccine is believed to be unable to trigger cellular and humoral immune responses, resulting in post-vaccination infections to occur (American Academy of Pediatrics 2018). An inactivated vaccine has constraints as it is unable to produce antibodies against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which plays a role in providing neutralization and protection from SARS-CoV-2 (Cucunawingsih *et al.* 2021).

The humoral and cellular immune response can be evaluated by examining peripheral blood CD4⁺ and CD8⁺ T cell percentages, respectively. In addition, the production of SARS-CoV-2 antibodies represents the ability of immune response toward vaccination in order to achieve protection and neutralization antibodies against SARS-CoV-2. This study aims to prove whether inactivated vaccines can trigger cellular dan humoral immune responses after primary doses of COVID-19 vaccination using inactivated vaccines (Mathew *et al.* 2020).

2 MATERIALS AND METHODS

2.1 Study population

This single-center cross-sectional study included a total of 50 healthcare workers who were admitted to Dr. Moewardi Hospital in Surakarta from February 2021 to June 2021 and underwent examination of peripheral blood CD4⁺ percentage, CD8⁺ percentage, and SARS-CoV-2 antibodies one-month following primary dose vaccination of COVID-19 using inactivated vaccine virus vaccine against SARS-CoV-2, CoronaVac. Two intramuscular doses of the vaccine were administered, with a 28-day gap. In order to decrease the influence of accompanying conditions which could affect the production of immune response, healthcare workers with a history of previous infection of COVID-19, aged over 60 years old, or below 18 years of age, prior to immunosuppressant therapy or malignant cancer therapy, immunocompromised condition, severe trauma, active infection, inflammatory and immunologic diseases, and malignant tumor were excluded.

2.2 Clinical data and laboratory assay

Basic clinical information was collected by resident doctors on admission and extracted from history taking by auto anamnesis.

Venous blood samples were collected for laboratory testing one month after receiving the second dose of the inactivated vaccine, CoronaVac vaccine. The subset of lymphocyte CD4⁺ and CD8⁺ T cell percentages were examined with BD FACSCanto™ II using the flowcytometry method. Roche Cobas® E411 with electro-chemiluminescence immunoassay (ECLIA) was employed for examining SARS-CoV-2 antibody.

2.3 Statistical analysis

Statistical analyses were performed by using SPSS® Statistics for Windows, Version 22. Statistical significance was set as $p < 0.05$.

Spearman's rank correlation analysis was performed to assess the correlation of CD4⁺ and CD8⁺ percentages with SARS-CoV-2 antibody. The correlation analysis was performed by examining the CD4⁺ and CD8⁺ percentages against the formed SARS-CoV-2 antibody to evaluate the degree of correlation strength of each T cell lymphocyte subset. The examination of the CD4⁺ and CD8⁺ T cell lymphocyte subsets on peripheral blood was used to assess the abilities of the humoral and cellular immune responses, respectively.

3 RESULTS

3.1 Characteristic of healthcare workers

The study subjects comprised 36 (72.0%) males and 14 (28.0%) females. The mean age was 33.46 ± 8.59 years, with a maximum age of 50 years old and a minimum age of 21 years old.

This study obtained the mean values of CD4⁺ percentage, CD8⁺ percentage, and SARS-CoV-2 antibody of 32.98 ± 7.74 , $27.72 \pm 8.58\%$, and $87.18 \pm 142.95\%$ U/ml, respectively. Characteristics findings are presented in Table 1.

Table 1. The baseline characteristics of the study subject.

Variable	F%	Mean + SD	(min-max)
Gender			
Male	14 (28.0%)		
Female	36 (72.0%)		
Age, years		33.46 ± 8.59	21.00–50.00
CD8 ⁺ (%)		27.72 ± 8.58	10.85–46.96
CD4 ⁺ (%)		32.98 ± 7.74	16.20–57.57
SARS-CoV-2 Antibody (U/ml)		87.18 ± 142.95	0.40–690.20

The mean of CD4⁺ T cell percentages was $32.98 \pm 7.74\%$, with a maximum percentage was 57.57% and a minimum percentage was 16.20%. This study also obtained the mean percentage of CD8⁺ T cells was $27.72 \pm 8.58\%$ with a maximum number was 46.96% and a minimum percentage was 10.85%.

Meanwhile, the mean value of the SARS-CoV-2 antibody was 87.18 ± 142.95 U/ml with a maximum value of 690.20 U/ml and a minimum value of 0.40 U/ml. A normality test was carried out with Saphiro-Wilk and the data of CD4⁺ and CD8⁺ percentages were within the normal distribution, while the number of SARS-CoV-2 antibodies was within an abnormal distribution. The Spearman's rank correlation test was carried out to evaluate the degree of correlation of the CD4⁺ and CD8⁺ percentages with the amount of SARS-CoV-2 antibody. We used Spearman's rank correlation test because we obtained variables with distributions that did not meet the assumption of normality after the Saphiro-Wilk test.

3.2 Correlation of CD4⁺ and CD8⁺ with antibody.

CD4⁺ percentage had a significant linear correlation with the SARS-CoV-2 antibody ($r = 0.322$, $p = 0.023$) (Figure 1). Meanwhile, the CD8⁺ percentage showed a significant negative correlation with the SARS-CoV-2 antibody ($r = -0.297$, $p = 0.036$) (Figure 2).

Correlation coefficients are presented in Table 2.

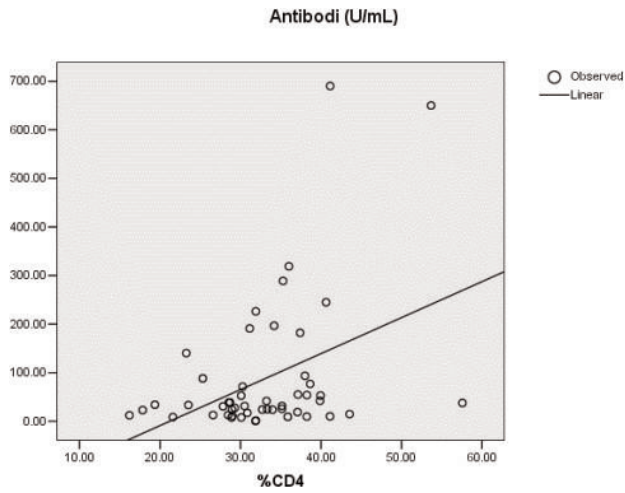


Figure 1. Correlation of CD4% percentage and SARS-CoV-2 antibody.

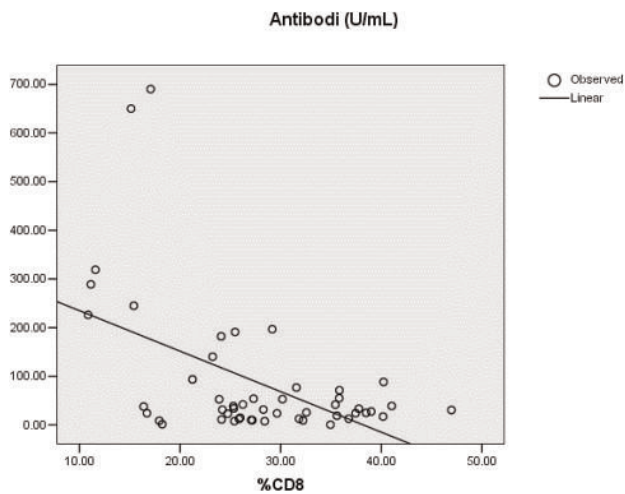


Figure 2. Correlation of CD8% percentage and SARS-CoV-2 antibody.

Table 2. Correlation coefficient.

Variable	r	SARS-CoV-2 antibody p-value
CD8 ⁺ (%)	-0.297	0.036*
CD4 ⁺ (%)	0.322	0.023*

* p-value from Spearman's Rank correlation test

* p < 0.05

4 DISCUSSIONS

In this study, a total of 50 healthcare workers following COVID-19 vaccination using two doses of inactivated vaccine CoronaVac were observed. We studied a humoral and cellular immune response after receiving the inactivated CoronaVac vaccine among healthy healthcare workers. It showed that the CD4⁺ percentage increased with an increase of SARS-CoV-2 antibody and was positively correlated with SARS-CoV-2 antibody, which indicated that the CD4⁺ percentage could represent the humoral immune response following COVID-19 vaccination.

This study revealed that there was a positive correlation between the CD4⁺ T cell percentage and SARS-CoV-2 antibody, which means that with every increase in the percentage of the CD4⁺, there is an increase in the number of SARS-CoV-2 antibodies. This correlation was statistically significant indicating that the increase proved that the inactivated vaccine can induce a humoral immune response following COVID-19 vaccination. This positive significant correlation demonstrates that inactivated vaccines can trigger a humoral immune response with a weak degree of strength. This can be used to answer doubts that inactivated vaccines cannot trigger a humoral immune response. Through this research, the authors prove that the inactivated type of vaccine given to healthcare workers in confronting the COVID-19 pandemic can trigger a humoral immune response which has implications for the ability to form post-vaccination SARS-CoV-2 antibodies, which can be expected as passive immunity in dealing with COVID-19 infection. Previous studies investigating CoronaVac's immunogenicity in immunosuppressed patients have yielded various results. For instance, Seree-aphinan *et al.* showed a suboptimal immune response and an appreciable level of the immune response following post-vaccination CoronaVac vaccine among adult dermatological patients receiving systemic immunosuppressive therapies (Seree-aphinan *et al.* 2021). On the other hand, Medeiros-Ribeiro *et al.* reported that in patients with autoimmune disease, the inactivated vaccine has shown a reduced yet acceptable level of immune response among autoimmune rheumatic disease (ARD) patients in which 56.3% of them develop detectable neutralizing antibodies post-vaccination without statistically significant difference in neutralizing activities with healthy controls (Medeiros-Ribeiro *et al.* 2021).

Meanwhile, this study found a weak negative correlation between the CD8⁺ percentage and the SARS-CoV-2 antibodies, meaning that any increase in the CD8⁺ percentage was not accompanied by an increase in the SARS-CoV-2 antibodies. This negative correlation was statistically proven in this study, indicating that these results did not occur by chance and it suggested that the ability of the COVID-19 inactivated vaccine to trigger a cellular immune response cannot be proven in this study. The ability of a vaccine to trigger a cellular immune response is an essential component in an individual's ability to form long-lasting antibodies that have protective and neutralizing abilities against an infection (Speiser & Bachmann, 2020). This study also showed that in study participants without prior SARS-Cov-2 infection, detectable antibodies were present after two doses of inactivated vaccine. A comprehensive review from Rabaan *et al.* in 2022 reported the persistence of humoral and cellular immune responses following six months post-vaccination. The antigen-specific CD4⁺ T cells had a higher detectable rate compared to CD8⁺ T cells in six months post-vaccination of inactivated COVID-19 vaccine (Rabaan *et al.* 2022).

The inability to prove cellular immune response after COVID-19 vaccination in this study indicates that inactivated vaccines may have a weakness in the ability to trigger a cellular immune response. Furthermore, the ability to trigger a cellular immune response is less than its ability to induce a humoral immune response. This study has several limitations. First, we only reported data from one month after the second vaccine dose. Second, we only evaluated the percentage of CD4⁺ and CD8⁺ towards SARS-Cov-2 antibody. Further study is needed using more specific markers of cellular immunity to assess the ability of inactivated vaccines to generate cellular immune responses.

5 CONCLUSIONS

In conclusion, this study presents immunogenicity data of the CoronaVac vaccine in a specific target group of healthy healthcare workers without previous history of COVID-19 infection following COVID-19 vaccination with inactivated CoronaVac vaccine first and second doses (primary dose). There are positive correlation of CD4⁺ percentage and a negative correlation of CD8⁺ percentage with SARS-CoV-2 antibody. This evidence that the inactivated COVID-19 vaccine CoronaVac (Sinovac Biotech Ltd., Beijing, China) can produce a humoral immune response. However, the finding of negative correlation indicates that the ability of this vaccine to induce cellular immune response has not been able to be proven. Further studies are needed to explore the immune responses with other specific immunological markers not presented in this study such as B-cells and NK-cells.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Health Research Ethics Committee Dr. Moewardi, Dr. Moewardi General Hospital. The participants provided their written informed consent to participate in this study.

CONFLICT OF INTEREST

There are no conflicts of interest.

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Increased level of TNF- α in serum and peritoneal fluid of endometriosis women-related infertility

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ABSTRACT: Endometriosis is a chronic inflammatory disorder characterized by abnormal endometrial tissue outside the uterine cavity, with a prevalence of 10% worldwide. TNF- α has been implicated in developing endometriosis; however, TNF- α is mainly unexplored in women with infertility cases. We aimed to evaluate serum and the peritoneal fluid level of TNF- α in endometriosis patients and correlate its level to the severity of endometriosis. Peripheral blood and peritoneal fluid samples were obtained from 87 infertility cases that underwent laparoscopy, consisting of 44 endometriosis women and 43 non-endometriosis women. We assessed serum and peritoneal fluid levels of TNF- α using an enzyme-linked immunosorbent assay. Serum and peritoneal fluid TNF- α levels were significantly increased in the endometriosis group compared to the control group (p-value = 0.0278; p-value = 0.0271). Serum and peritoneal TNF- α levels significantly differed between late-endometriosis and the control group (p-value = 0.026, p-value = 0.004). Our results show increased levels of TNF- α level in endometriosis women related to infertility cases that correlate with the severity of endometriosis.

1 INTRODUCTION

Endometriosis is a chronic inflammatory disorder affecting ~180 million women worldwide (Horne & Saunders 2019). This disease affects 5–10% of reproductive-age women and 30–50% of women who experience infertility (Giudice 2004). Endometriosis is characterized by the growth of abnormal endometrial tissue outside the uterus. The major symptoms of endometriosis are pelvic pain, dysmenorrhea, and dyspareunia (Horne & Saunders, 2019). Until now, the classification of endometriosis is mainly determined by the revised American Society for Reproductive Medicine (rASRM). This system is measured according to the extent of adhesions, localization, and size of implants (Tanbo & Fedorcsak 2007). Unfortunately, the rASRM classification does not predict a woman's fertility (Guzick *et al.* 1997). Endometriosis Fertility Index (EFI) is also useful for the clinician to predict the pregnancy outcome. This system combines the measurement based on the rASRM score with additional anamnestic and post-surgical information (Adamson & Pasta 2010).

Until now, the exact pathogenesis of endometriosis remains unclear. It has proven challenging for clinicians, gynecology and reproduction specialists, and researchers. One theory that has been

widely accepted to explain the pathogenesis of endometriosis is Sampson's retrograde menstruation (Kapoor, 2021). It defines a backflow of menstrual blood and cells inside the peritoneal cavity. The pathogenesis of endometriosis also occurs due to several features, such as altered immunity, aberrant endocrine signaling, ectopic endometrial tissue, genetic factors, and unbalanced cell proliferation and apoptosis. Moreover, several inflammatory molecules play an important role in initiating endometriosis and its associated symptoms, such as infertility and pain (Taylor 2021).

Inflammation is a major mechanism that stimulates any disease, including endometriosis. In the case of endometriosis, inflammation is involved in cell proliferation and infiltration. This condition activates several immune cells in the uterine environment, such as macrophages, natural killer cells, and T cells. The immune cells are associated with increased proinflammatory mediators such as cytokines (García *et al.* 2019). Tumor necrosis factor-alpha (TNF- α) is a major proinflammatory cytokine associated with endometriosis's pathogenesis. TNF- α is secreted by peritoneal macrophages in endometriosis, increasing the permeability of local blood vessels. It causes aggravation of peritoneal inflammation and inflammatory exudation into the peritoneal cavity (Tao *et al.* 2011). Furthermore, TNF- α triggers adhesion to peritoneal cells and stimulates endometrial cell proliferation and angiogenesis (Bedaiwy *et al.* 2002; Pizzo *et al.* 2002). The high level of TNF- α affects an embryotoxic effect and sperm motility *in vitro*, causing infertility in endometriosis (Soave *et al.* 2015).

Limited studies explored TNF- α in endometriosis-related infertility cases. In a present study, we examine TNF- α levels in serum and peritoneal fluid among infertile women, including endometriosis women and women with a single benign gynecologic disorder related to the fallopian tubes, fibroids, or ovaries.

2 MATERIALS AND METHODS

2.1 Study design

Forty-four cases of endometriosis and forty-three control women were recruited. The classification of endometriosis was scored according to the revised American Fertility Society (rAFS) classification. Endometriosis patients in stages I and II were classified as the early endometriosis group ($n = 19$), while those in stages III and IV were classified as the late endometriosis group ($n = 25$). The Control group included women with a benign gynecologic disorder related to the fallopian tubes, fibroids, or ovaries. The inclusion criteria were endometriosis women who underwent laparoscopy of reproductive age for the case group. Exclusion criteria included having hormonal medications and immunosuppressive drugs within the last three months, having more than a single gynecological disorder, unexplained infertility, or having pelvic inflammatory disease (PID). The institutional ethics committee, Faculty of Medicine, Universitas Airlangga, Surabaya, Indonesia, approved the study, and all enrolled cases received informed consent and gave their written consent.

2.2 Sample collection

Blood samples were obtained preoperatively from all study participants before laparoscopic surgery. Blood samples were centrifuged at 3000 rpm, 4°C for 10 min. Then, peritoneal fluid was aspirated from the pouch of Douglas during the laparoscopic direct vision by aspiration needle. Peritoneal fluid samples were centrifuged at 1000 rpm, 4°C for 10 min. The supernatant was taken and placed into 1.5 mL centrifuge tubes. All samples were labeled and stored at -80°C in aliquots until further analysis.

2.3 Clinical and demographic parameters

Clinical information was assessed based on the rASRM adhesion score, rASRM endometriosis score, and total EFI score for endometriosis patients. Demographic parameters, including the age, type of infertility, length of infertility, and dysmenorrhea of patients, were recorded in all participants.

2.4 TNF- α measurement

TNF- α level in serum and peritoneal of endometriosis patients and controls were measured by an enzyme-linked immunosorbent assay (ELISA) kit provided by R&D Systems, Minnesota, USA, according to the manufacturer's instructions. Each sample was measured in duplicate. The level of TNF- α was shown as pg/mL.

2.5 Statistical analysis

The differences between the control and endometriosis groups were measured by the two-tailed Mann-Whitney U test. Data comparisons between three or more groups were evaluated by the Kruskal-Wallis rank test. The spearman's rank correlation correlations were used to measure two continuous variables and represented as rho (r). The rho value determined the strength of correlations with $r < 0.2$ = weak, $0.4 > r \geq 0.2$ = moderate, and $r \geq 0.4$ = strong. All statistical analysis was done using GraphPad Prism version 8.01. A p-value of < 0.05 was considered statistically significant.

3 RESULTS

3.1 Demographic characteristics

The characteristics of clinical and demographic variables among endometriosis cases and controls are shown in Table 1. The analyzed data showed no significant difference in age, length of infertility, and dysmenorrhea of patients.

Table 1. Patient's characteristics.

Variables	Endometriosis (n = 44)	Gynecologic control (n = 44)	p-value
Age (years) ^a	30 (27 –36)	30 (27 – 35)	0.530 ¹
Dysmenorrhea ^b	25 (54.55%)	23 (53.49%)	0.752 ¹
Length of infertility (year) ^a	4 (1 – 6)	4 (1 – 7)	0.367 ¹

Data shown as ^a median (25%–75% percentile), and ^b frequency (percentage). Statistical analysis performed with two-tailed Mann-Whitney U; * p-value < 0.05 .

3.2 The levels of TNF- α in peritoneal fluid and serum

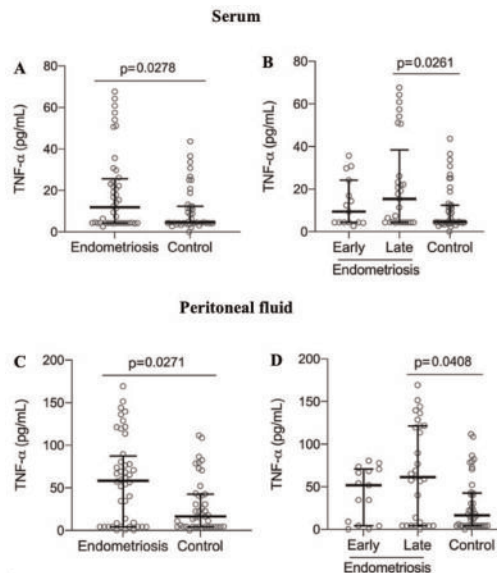


Figure 1. Peritoneal fluid and serum levels of TNF in endometriosis and gynaecologic control patients.

The levels of TNF- α in scattering dot plot graphs with medians and interquartile ranges are shown according to (A) the endometriosis versus control groups, (B) the severity of endometriosis and control cases in serum, (C) the endometriosis versus control groups, (D) the severity of endometriosis and control cases in peritoneal fluid. The groups were compared using a two-tailed Mann-Whitney U test. Each dot represents a single subject. Significant p -values are indicated.

TNF- α level in serum was significantly different between the control and endometriosis groups ($p = 0.0278$, Figure 1A). Furthermore, we measured the TNF- α level based on the severity stage of endometriosis. The TNF- α level was significantly different between patients with late endometriosis compared to the control group ($p = 0.0261$, Figure 1B). Peritoneal TNF- α level also showed significantly higher in endometriosis patients compared to the control group ($p = 0.027$, Figure 1C). The late endometriosis had a higher level of TNF- α in peritoneal fluid than the control group ($p = 0.0408$, Figure 1D).

3.3 The levels of TNF- α in endometriosis and three groups of gynaecologic control patients

We further evaluated TNF- α levels among the control group-fallopian, ovary, or myoma-related infertility. No apparent difference was found in serum and peritoneal fluid of TNF- α among the endometriosis group and the control group-fallopian, ovary, or myoma-related infertility (Figure 2A–B).

Serum TNF- α (A), peritoneal fluid TNF- α (B) in four groups of infertility cases (endometriosis group and three control groups: Fallopian-, ovary-, and myoma- related infertility)

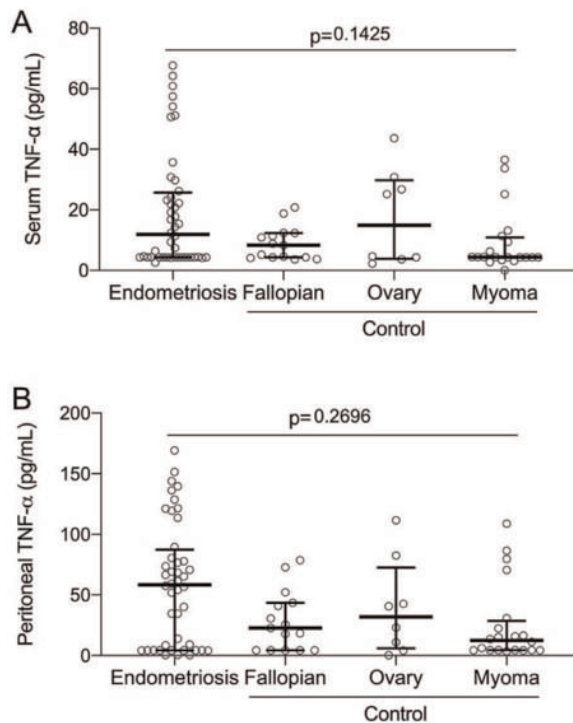


Figure 2. TNF- α level in the endometriosis group and the gynaecologic control patients.

are presented. The groups were compared using the Kruskal-Wallis rank test. Significant p -values are indicated.

3.4 Correlation between $TNF-\alpha$ level among clinical parameters

In patients with endometriosis-related to infertility, no significant correlation was found between $TNF-\alpha$ level [$r = 0.122$, $p = 0.259$] with rASRM adhesion score (Figure 3A). In terms of rASRM endometriosis score, we found no correlation of $TNF-\alpha$ with rASRM endometriosis score [$r = -0.068$, $p = 0.660$] (Figure 3B). As shown in Figure 3C, there was not a significant correlation of $TNF-\alpha$ with total EFI score [$r = 0.0008$, $p = 0.993$].

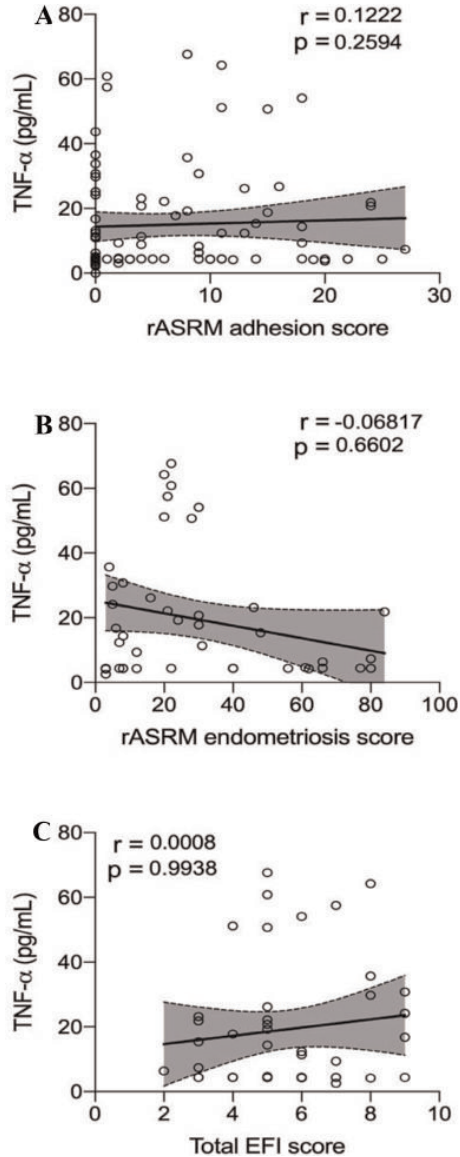


Figure 3. Spearman's correlation analysis of $TNF-\alpha$ in serum.

The correlations between the TNF- α and rASRM adhesion score (A), rASRM endometriosis score (B), and total Endometriosis Fertility Index (EFI) score (C) are presented. The graphs show rho (r) values, *p*-values, regression line, and error band. Each dot represents one subject.

4 DISCUSSION

Herein, we demonstrated that TNF- α is involved in the progression of endometriosis-related infertility. As expected, late endometriosis had the highest TNF- α level in serum and peritoneal fluid compared to the control group. Our findings suggest that the severity of endometriosis correlates with TNF- α level in serum and peritoneal fluid of women with endometriosis-related infertility.

Several researchers have evaluated the role of several cytokines in serum and peritoneal fluid of endometriosis patients (Bedaiwy & Falcone 2004; Kalu *et al.* 2007; Othman *et al.* 2008). The pro-inflammatory cytokines in the peritoneal fluid are higher in women with endometriosis compared to the control group. The pro-inflammatory state fosters the development and growth of endometriotic lesions. Furthermore, differences in the serum level of cytokines have been reported in endometriosis cases (Herington *et al.* 2011; Matalliotakis *et al.* 2003). TNF- α has been reported as a pluripotent mediator. It plays a critical role in the peritoneal cavity of women with endometriosis (Sakamoto *et al.* 2003). In agreement with the previous result, our findings reveal that peritoneal and serum TNF- α levels are positively correlated with the severity of endometriosis (Richter *et al.* 2005; Xavier *et al.* 2006). A study has shown that serum TNF- α levels increased three times in endometriosis patients (Tarokh *et al.* 2019). A recent report the higher level of TNF- α in the peritoneal fluid of late endometriosis patients compared to early endometriosis patients (Ragad *et al.* 2022). The peritoneal fluid (PF) is a dynamic environment closely associated with the immune system. Soluble molecules in PF are affected by the presence of endometriosis. Accumulated cytokines and growth factors interfere with fertility. Activated macrophages release several cytokines, such as TNF- α , which cause various effects, including cytotoxicity. Activation of macrophages and endometriosis-associated infertility is related to the increased production of TNF- α (Oral *et al.* 1996).

Infertility in endometriosis patients can be caused by anatomical distortions, adhesions, and immunological disturbances (Tanbo *et al.* 2017). Altered peritoneal function, distorted pelvic anatomy, ovulatory abnormalities, and altered immune cell-mediated functions in the endometrium also cause infertility in endometriosis patients (Bulletti *et al.* 2010). Furthermore, systemic immune modification has been reported in the progression of endometriosis. This condition triggers the activation of peripheral blood monocytes, which secrete high levels of cytokines such as TNF- α (Kany *et al.* 2019). Our current result reveals a significant increase in serum levels of TNF- α among women with endometriosis who underwent laparoscopy. Increased levels of cytokines in the serum and peritoneal fluid of endometriosis women may reflect the increased synthesis of cytokines by ectopic endometrial implants, macrophages, and peritoneal lymphocytes (Králičková & Větvicka 2015). Furthermore, high expression of TNF- α has been reported to affect sperm motility *in vitro* and have an embryotoxic effect (Jayaprakasan *et al.* 2017). These findings suggest that TNF may have an important role in the development of infertility related to endometriosis (Soave *et al.* 2015).

5 CONCLUSION

The severity of endometriosis related infertility associated with the level of TNF- α . Further studies are needed to investigate the mechanism of TNF- α in endometriosis-related infertility to improve our understanding on the immunopathogenesis.

ACKNOWLEDGMENT

This work was supported by the internal research grant of the Faculty of Medicine, Universitas Airlangga, Indonesia.

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Integrated Clinical Clerkship (ICC) learning environment: How it correlates with pre-service medical doctors' career choice

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ABSTRACT: Pre-service medical doctors have several career choices once they graduate from the faculty of medicine. Their choices may be influenced by several factors, including the learning environment. This current study aims to seek a correlation between the medical students' perceptions of integrated clinical clerkship as the learning environment and career choices. This cross-sectional study was conducted at Indonesian Red Cross offices involving 160 medical students by using a consecutive sampling technique. This study employed the Postgraduate Hospital Educational Environment Measure (PHEEM) questionnaire which is valid and reliable by values of 0.89 ($\alpha = 0.826$) and $r \geq 0.30$ ($r = 0.442$). The data were analyzed using the Wilcoxon Theta Correlation test for nominal and ordinal measurement scales. The result of career choice shows that most of the students choose a non-primary care doctor career. There is a weak correlation between the integrated clinical clerkship (ICC) learning environment at the Indonesian Red Cross and the choice of a career as a primary care doctor for students with a value of $\theta = 0.0084$ ($\theta < 0.2$). There is a weak correlation between the ICC learning environment at the Indonesian Red Cross and career choices as a primary care doctor.

1 INTRODUCTION

One of the health-system issues that occurs in various countries in the world is the distribution of health workers, including general practitioners. The availability of medical workers is influenced by the career choices of medical students during the learning process which can have an impact on the distribution of medical workers, future lives, and the health development system (Fedrian *et al.* 2016).

The choice of a career as a specialist is still the first choice compared to being a doctor who works in primary health care or as non-clinicians, although there are still those who choose to work as primary care doctors (Querido *et al.* 2018). The career selection process is determined by eight categories and is carried out from the first year of entering medical school until completing his clinical rotation (Cui *et al.* 2021).

The integrated clinical clerkship (ICC) is part of the clinical rotation that must be carried out by students of the Medical Profession Study Program of Faculty of Medicine in Indonesia to provide opportunities for young doctors to practice as general practitioners in a comprehensive manner after gaining knowledge at the departmental clinic rotation stage. It is also to sharpen social sensitivity, and build Inter-Professional Education (IPE) and Inter-Professional Collaboration (IPC). It supports the vision of medical faculties to produce alumni who are oriented toward

community health. At this stage of activity, medical students carry out community-based activities to provide health services directly every week with the aim of helping people who are quite far from sufficient health services (Torres-Roman *et al.* 2018).

Role models have an influence in determining career choices, while academic motivation has a non-significant relationship with career choices in medical faculty students (Roff *et al.* 2005). However, this research aims to analyze the relationship between career choices as primary care physicians for students of the medical profession study program and the learning environment at the ICC, especially the one carried out by the Indonesian Red Cross (IRC).

2 METHODS

This research data was taken from August 2020 to December 2021 at IRC offices in Central Java, Indonesia. This study used a cross-sectional approach. The population of this study were all students of the Medical Profession Study Program, Faculty of Medicine who took ICC at the IRC office. The researchers took samples from the population in accordance with the inclusion and exclusion criteria that have been set by using consecutive sampling techniques in order to obtain 160 respondents.

The samples of this study were taken based on the inclusion criteria, namely the respondent had completed the rotation of the ICC at the IRC office for less than one month before data collection and were willing to fill out the questionnaire. Incompletely filled-out questionnaires were not included in the research data. Data on students' perceptions of the learning environment were obtained from filling out a questionnaire adapted from the *Postgraduate Hospital Educational Environment Measure (PHEEM)* questionnaire.

PHEEM is a questionnaire developed by Roff *et al.* to assess various aspects of the clinical learning environment for residents in the United Kingdom (Roff *et al.* 2005). In the PHEEM questionnaire validity test, it was found that the Pearson correlation coefficient (r) = 0.442 which means it is valid (valid if $r > 0.30$). The reliability test obtained from Cronbach's Alpha for PHEEM was 0.826 which means reliable (reliable if α ranges from equal to or more than 0.6) (Sugiyono 2014).

The measurement was expressed in a ratio scale which is converted into a nominal scale with the classification of very poor, many problems, better (needs improvement), and very good. Data about the respondents' career choices were filled together with PHEEM questionnaire filling. Career options involved specialists/subspecialists, academics/researchers, health managers/policy stakeholders, and other career options. The measurement scale is expressed in a nominal scale. Data analysis used the Wilcoxon Theta Correlation test to determine whether there was a relationship between perceptions of the ICC learning environment and the career choices of medical students (Priyanto 2014).

3 RESULTS

Characteristics of research respondents are described in Table 1.

Table 1. Characteristics of research respondents.

Criteria	Frequency (n)	Percentage (%)
Sex		
Male	34	29,9%
Female	80	70,1%
Age (year)		
23	1	0,8%
24	17	14,9%
25	33	28,9%
26	50	43,9%
27	9	7,9%
28	2	1,8%
29	2	1,8%

(continued)

Table 1. Continued

Criteria	Frequency (n)	Percentage (%)
Motivation to be medical students		
Self-motivated	83	72,8%
Parents	28	24,6%
Others	3	2,6%
Year of profession program		
2013	1	0,9%
2016	15	13,1%
2017	71	62,3%
2018	27	23,7%
Bachelor's GPA		
3,00 – 3,50	100	87,7%
3,51 – 4,00	14	12,3%

The interpretation of the total PHEEM score is explained in Table 2.

Table 2. Distribution of the respondents based on the perceptions of the clinical learning environment.

PHEEM score	Interpretation	Frequency(n)	Percentage (%)
0–40	Very poor	0	0%
41–80	Many problems	10	8,8%
81–120	Better (needs improvement)	95	83,3%
>121	Very good	9	7,9%

The results of the PHEEM score at the integrated station at the IRC office obtained the lowest score of 66 and the highest score of 137. Based on the results of the assessment of the clinical learning environment, most responses are in a good category or needs improvement. Based on the data obtained, the results of the different PHEEM sub-scale scores were obtained. The interpretation of the results of the PHEEM sub-scale scores is described in Table 3.

Table 3. The distribution of respondents based on ICC learning environment perception.

PHEEM Total score	Interpretation	Frequency (n)	Percentage (%)
<i>Autonomy</i>			
0–12	Very bad	0	0,00
13–24	Having negative perceptions on his roles	8	7
25–48	Having positive perceptions on his work	106	93
>48	Having very positive perceptions on his work	0	0,00
<i>Perception of teaching</i>			
0–15	Very bad quality	0	0,00
16–30	Need further training	8	7
31–45	Improving	87	76,3
>45	High-quality lecturer	19	16,7
<i>Perception of Social Support</i>			
0–10	Nothing	0	0,00
11–20	Unpleasant place	10	8,8
21–30	More supports than contradiction	92	80,7
>30	Very supportive environment	12	10,5

3.1 Characteristics of career choice outcomes

In this study, career choices included primary care physicians at health facilities I (community health service/clinics) and non-primary care physician careers consisting of doctors at health facilities II (hospitals), academicians/researchers, health managers/policymakers, and other careers (non-health self-employment and careers outside the medical field). Respondents can only choose one career choice.

Table 4. Frequency distribution of respondents based on career choices.

Career choices	Frequency (n)	Percentage (%)
General practitioner in health facilities I	13	11,4%
General practitioner in health facilities II	77	67,5%
Academicians/researchers	9	7,9%
Health managers/policymakers	10	8,8%
Others	5	4,4%

3.2 Data analysis

The data obtained from the research results were further analyzed. In the comparative bivariate analysis test, a chi-square test was carried out and the following data were obtained.

Table 5. Results of data analysis using the chi-square test.

Career choices		Learning environment			Total
		BM	BBP	SBA	
DFI	<i>Count</i>	2	9	2	13
	<i>Expected count</i>	1.1	10.8	1.0	13.0
DFII	<i>Count</i>	6	65	6	77
	<i>Expected count</i>	6.8	64.2	6.1	77.0
A/P	<i>Count</i>	0	9	0	9
	<i>Expected count</i>	0.8	7.5	0.7	9.0
MK/PK	<i>Count</i>	2	8	0	10
	<i>Expected count</i>	0.9	8.3	0.8	10.0
Others	<i>Count</i>	0	4	1	5
	<i>Expected count</i>	0.4	4.2	0.4	5.0
Total		10	95	9	114.0

DFI = doctor at health facility I; DFII = doctor at health facility II; A/P = academicians/researchers; MK/PK = health manager/policy makers; SBU = very bad; BM = lots of trouble; BBP = good but need improvement; SBA = very good

In Table 5, it is found that the expected count value < 5 is 6 (more than 20% of the contingency table). Furthermore, the Wilcoxon Theta Correlation Test was carried out and the correlation value 0.0084 was obtained. According to Gulliford's criteria, this value is interpreted as a weak correlation.

4 DISCUSSION

The results of this study indicate that the perception of the ICC learning environment has a weak correlation with career choice with value strength ($\theta = 0.0084$), where the ICC learning

environment does not correlate with the choice of one's career as a primary care physician. It indicates that the independent variable is not the only factor that affects the dependent variable (Rukmini & Bogar 2021). Additional variables can affect the validity of the study. Several additional variables that influence include age, gender, year of admission to the ICC, reasons for entering the medical faculty, and length of time participating in the ICC. In addition, personal interests, role models, personality types, and characteristics of each career also have an influence.

The average respondents' perception of the IS learning environment is in the "good but still in need of improvement" (BBP) category, which was 95 respondents (83.3%). These results have similarities with a study conducted on 72 urology residents at King Saud University, Saudi Arabia (Alkhamees *et al.* 2021). The results showed that the overall perception of the clinical learning environment was good, but there were still important aspects to improve. The similarities in the results of this study can occur due to several factors, including the atmosphere of cooperation in the educational environment and easy-to-find field supervisors. Based on the results of the open-ended questionnaire, several themes were figured out to improve the implementation of the clinical education environment at PMI Surakarta including guidebooks for students, clear learning outcomes by field supervisors, and proper eating facilities when on guard.

The results of the PHEEM measurement on the autonomy sub-scale showed that as many as 106 students (93%) had a positive perception of their work. The results of the assessment on the aspects of autonomy stated that the majority of students had a good view of their work. This relates to the responsibilities given in accordance with the level of competence and makes them more ready to go to the next career level. Several factors influence a good view of work, including getting responsibilities according to the level of work, feeling part of a work team, and feeling that learning activities support the respondent to be better prepared to face the next career levels.

In the perception of teaching sub-scale, most students, namely 87 respondents (76.3%), had the perception that the ICC learning environment had a positive influence, followed by 19 respondents (16.7%) perceived that the lecturers had set an example. In the perception of teaching sub-scale, the majority of students perceived that the teaching in the learning environment had been carried out according to standards. Problems that occur in the learning environment are the lack of teachers, unclear learning outcomes, and lack of access to educational programs that are relevant to needs.

The results of the assessment on the aspect of perception of social support showed that the majority of students, 92 students (80.7%), had a perception of social support in the form of more pros than cons. This aspect is supported by a good culture of cooperation between respondents in one group. The positive effects of this perception include the respondent getting advice that supports a career, feeling safe in the learning environment, a lack of a culture of blaming each other, and the ability to still enjoy life outside the learning environment.

4.1 Career choices

The results showed that most of the respondents were female than male with the majority of the Bachelor's GPA ranging from 3.00 to 3.50. However, there is no relationship between gender and GPA with career choice (Winkel *et al.* 2021). In addition, the study showed that most of the respondents chose a career as a doctor in non-primary services, namely hospitals with 77 respondents (67.5%) (Torres-Roman *et al.* 2018). Factors that influence this include the respondent having the opportunity to do clinical research and perform medical procedures that require special skills, lead a more active life rhythm, more challenging places to work such as the Emergency Room (IGD) and Intensive Care Unit (ICU), higher social status, and also a greater income.

Respondents who chose a career as a doctor in primary care in this study were 13 respondents (11.4%). The lack of students who have an interest in careers in primary care can be a concern for policymakers, especially in the current era of National Health Insurance where primary care is the frontline of the Indonesian nation's health. Students' ignorance about a career will affect their career choices so students only choose the type of career that they know and follow the current trend. The literature on personality and career choice explains that personality types will affect a person's career choice and performance during a career (Hussain 2012).

Some respondents answered more than one career choice. This phenomenon regarding career choice has two possibilities: Either the career choices have not been specified, or the majority of respondents choose to pursue more than one career in the future. Education providers need to pay attention to this phenomenon to be taken into consideration in fostering and managing student careers. Educational policyholders can also provide students with various soft skills that can support students in their future careers, either with one type of career or several careers at once such as leadership, time management, problem management, collaboration, communication, adaptation, and others. In addition, education providers can also provide information that must be prepared by students in careers outside primary and non-primary services such as further studies, scholarships, recruitment requirements, and other things that can support career preparation outside primary and non-primary services.

5 CONCLUSION

There is a weak correlation regarding the relationship between the ICC learning environment with career choices as primary care physicians. Students' ignorance about a career will affect their career choices so students only choose the type of career that they know and follow the current trend. The literature on personality and career choice explains that personality types will affect a person's career choice and performance during a career.

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Medical nutrition therapy in inguinal squamous cell carcinoma and cardiorenal syndrome undergoing hemodialysis: A case report

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ABSTRACT: Malignancy can lead to kidney and heart disorders through the number of mechanisms. Severe disturbance of renal function requires kidney replacement therapy such as hemodialysis. This process induces protein energy-wasting conditions that reduce quality of life. A 51-year-old male patient diagnosed with acute on chronic kidney disease on hemodialysis, obstructive nephropathy, inguinal squamous cell carcinoma, deep vein thrombosis, history of congestive heart failure fc III. The patient underwent nutritional therapy by getting energy started from 20 kcal/kg body weight/day. The administration of protein starting from 0.9 g/kg body weight, and it is adjusted on dialysis status and urea level because giving protein intake > 1 g/kg body weight results in increasing the urea level of the patient. Since there were water intake restrictions, food's form changing has given more benefit to the patient. Nutritional therapy is needed to support the quality of life, reduce length of stay, and prevent further malnutrition.

1 INTRODUCTION

Chronic kidney disease (CKD) is characterized by a progressive and persistent decrease in renal function followed by hemodialysis (HD) in the late stage (Heng & Cano 2010). Cancer could lead to CKD through several mechanisms, and 12% of 4,684 cancer patients—who average 58 years old—have a glomerular filtration rate (GFR) less than 60 ml/min/1.73m² (Stengel 2010; Stevens *et al.* 2013). Renal dysfunction will increase mortality and the incidence of heart disease morbidity. The Hemodialysis study states that 40% of CKD patients will develop ischemic heart failure, a condition known as cardiorenal syndrome, which leads to mortality of CKD patients 10–20 times higher than the general population (Uduman 2018).

The mortality rate will continuously increase if not treated immediately. Hemodialysis becomes one of therapy for CKD patients who experience cardiovascular dysfunction. Nevertheless, quality of life will decrease, especially when fluid and protein restrictions (Wong *et al.* 2017). Research by Ravel *et al.* (2013) showed that a low-protein diet in CKD patients on HD was associated with mortality increase. This is in accordance with Shinaberger *et al.*, (2006) which states that protein administration of 1.0–1.4 g/kg BW/day shows a better survival rate when compared to lower protein. Thus, nutritional therapy should be carried out as one of the kidney protection strategies together with other therapies and medical considerations, and diet modification based on the clinical setting is important to improve the patient's nutritional status (Zha & Qian 2017).

2 CASE HISTORY

A 51-year-old male patient consulted to clinical nutrition department with a clinical diagnosis of acute CKD on HD due to obstructive nephropathy, inguinal squamous cell carcinoma, venous thrombosis (deep vein thrombosis or DVT), and history of congestive heart failure (CHF) fc III. Four years earlier, the patient was diagnosed with inguinal cancer and then completed chemotherapy and radiation therapy. Two years later, new malignancies were found around the bladder followed by urination disturbances, which urged the patient to get another chemotherapy that induced several symptoms such as nausea, vomiting, urinary disorders, and swelling on both legs of the patient. One month before being admitted to the hospital, the patient experienced shortness of breath. After some prescriptions and no meaningful changes, the patient was put on HD therapy. Based on nutritional and gastrointestinal history, the patient's appetite was reduced with a repeated occurrence of nausea, vomiting, and canker sores. Since the patient takes cancer-specific oral nutritional support (ONS), the intake decreases to 12–16 kcal/kg body weight (BW) and about 0.2 g/kg BW protein derived from a full liquid diet.

According to the physical examination, the patient's vital signs are stable with oxygen support and various medications. Signs of muscle wasting were found in both areas of the upper extremities, otherwise swelling in both lower extremities. The functional capacity was assessed by estimating the hand grip power and calculating the Karnofsky score (the first score result was 30). The estimated BW is 58 kg, so the body mass index was 22.1 kg/m². There was a 14% loss of body weight or about 10 kg of estimated BW over the past six months. The laboratory test was done two days before the consultation. It indicated anemia, leukocytosis, uremia, low eGFR, and hypoalbuminemia. Based on the thoracic roentgen, cardiomegaly and left pleural effusion were declared. The ultrasound examination ensures obstruction on both kidneys and DVT in the bilateral distal femoral veins, and the electrocardiography showed a 60% ejection fraction accompanied by the left atrium dilatation. Due to the absence of daily diuresis, the patient's fluid balance was positive.

Patients are given nutritional therapy in purpose to gradually increase calorie and protein intake, especially during HD. Since water intake was limited by the doctor in charge, changing the form of food has given more benefit to this patient. The full liquid diet slowly changed to thicker and solid foods, and by increasing the viscosity, higher energy and protein intake was finally obtained. The average energy intake was 15–25 kcal/kg BW, protein 12%–17% (0.5–1.1 g/kg BW), fat 17%–28%, and carbohydrates 55%–70%. The optimal protein intake was 0.8 g/kg BW/day since the administration of protein > 1 g/kg BW/day increased the patient's urea level. The patient was discharged home after a nephrotomy procedure followed by improvement of clinical symptoms, appetite, and increase of functional capacity (the final Karnofsky score was 50).

3 DISCUSSION

Patients diagnosed with end-stage CKD are at substantial risk of getting nutrition disorders and malnutrition. In kidney disorders, malnutrition is associated with a decrease in energy and protein storage in the body, or to The International Society of Renal Nutrition and Metabolism known as “protein-energy wasting” (Fiaccadori *et al.* 2021). Impaired energy and protein stores in the body occur due to decreased intake, changes in assimilation or use of nutrients, and hyper-catabolism due to comorbidities. In HD patients, the protein catabolism increases due to the loss of amino acids and albumin into dialysate and inflammatory processes triggered by the dialysis procedure. Thus, progressive depletion of energy and protein will occur along with renal dysfunction (Fiaccadori *et al.* 2021; Oliveira *et al.* 2019).

Various clinical evidence proves that nutritional therapy provides beneficial effects in CKD patients with a numbers of comorbid. To fulfill it, the amount of energy intake needed

to be estimated using indirect calorimetry (remains as the gold standard). However, due to limited facilities and costs, the Harris-Benedict formula is often used. Energy and protein amounts were really depending on the comorbidity and dialysis status of the patient. The patient's basal metabolic rate (BMR) is known to increase by 12%–20% during dialysis (Fiaccadori *et al.* 2021; Oliveira *et al.* 2019). BMR of this patient was 1330 kcal or 23 kcal/kg BW, while the total daily energy expenditure was 1995 kcal or 34 kcal/kg BW. The amount met the recommendation of KDIGO (30–35 kcal/kg BW/day). Patients diagnosed with severe heart failure need a total energy of 30%–50% higher than BMR to meet more energy requirements due to an increase in cardiopulmonary activity. Moreover, the amount of protein intake is also one of the important factors in HD patients. However, daily protein intake is also individual since it needs to be adjusted to the nutritional status, phosphate level, and dialysis effect. Protein administration will vary in CKD patients, but it is expected the patient could reach at least 0.3–0.4 g /kg BW/day orally at the beginning of the treatment. While undergoing the dialysis process, protein intake can increase up to 1.2 g/kg BW /day and 50% of it should be the high biological value source (Oliveira *et al.* 2019).

Water intake restriction has been more challenging in feeding this patient. By changing daily food's form, the patient finally gets more energy and can enjoy his feeding process. Food form influences both appetitive and nutritional relevant physiological processes for important energy balance (Forde & Bolhuis 2022). The average energy intake of this patient was 15–25 kcal/kg BW. At the beginning of the treatment, the patient could obtain protein intake as recommended (0.2–0.3 g/kg BW/day). However, in the dialysis process, higher protein intake was not obtained because of several clinical obstacles. Thus, optimal protein intake has been 0.8 g /kg BW /day since the patient's urea level was increased along with higher protein intake (protein >1 g/kg BW /day). Increasing the protein intake induces a series of adaptive processes. The most conspicuous adjustment is an increase in amino acid oxidation and in subsequent nitrogen excretion, mainly as urea, known as the final product of amino acid metabolism. Through the process of catabolism, proteins break down into amino acids and deaminate ammonia, which will subsequently be synthesized into urea mainly in the liver. Furthermore, its excretion depends on the filtration function of the glomerulus. Urea has toxic properties so when not excreted from the body, it can cause uremia (Weiner *et al.* 2015).

4 CONCLUSION

Diet modification based on clinical setting is part of nutritional therapy which could improve a patient's clinical status. Based on this case report, it is important to pay attention to clinical conditions and laboratory marker changes to ensure optimal nutrition. Food form changing in a patient with water intake restriction has more benefits.

CONFLICT OF INTEREST

The author declares that there is no conflict of interest whatsoever in the preparation of the case report in this manuscript.

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Medical nutrition therapy as an influencing factor on nutritional status and functional capacity improvement of tuberculous meningitis patients: Case report

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ABSTRACT: Tuberculous Meningitis (TBM) is the most severe manifestation of Tuberculosis infection attacking the central nervous system (CNS) and causing risk of malnutrition in patients due to the decreasing ability to eat and loss of appetite. We focused on the nutritional aspect of TBM patients and its significance in patient health outcomes. We describe a 35-year-old Asian male who was diagnosed with Tuberculous meningitis and had been hospitalized in the neurology ward at Cipto Mangunkusumo Hospital Jakarta. The patient had a headache, dizziness, and seizure. After being diagnosed with TBM, the patient was then consulted by the Clinical Nutrition Department due to malnutrition appearance. The patient was observed and given high energy protein intake. Nutritional status based on anthropometric indices did not change during observation, but there were improvements in total lymphocyte count and functional capacity.

1 INTRODUCTION

Tuberculous meningitis (TBM) has been the most severe clinical manifestation of extrapulmonary tuberculosis infection. It has been known to affect 10,4 million new TB cases worldwide and 51% of them develop disability and death (Kumar *et al.* 2016; World Health Organization 2016). Data from the Indonesian cohort showed that 34% of brain infections were caused by TBM (Imran *et al.* 2018; Thwaites *et al.* 2002). Loss of consciousness and neurologic deficit in TBM patients causes disturbances in chewing and deglutition function increasing the risk of malnutrition, morbidity, and mortality, as well as decreasing functional capacity (Casanan *et al.* 2017; Thwaites & Hien 2005; Kelly & Buchholz 1996; Macallan 1999; Misra *et al.* 2011).

In this case report, we discussed a TBM patient with severe malnutrition and had some improvement after treatment and clinical nutrition management. This report highlighted the importance of nutritional support in TBM patient which emphasized protein intake in order to avoid further malnutrition which influence the increase of morbidity.

2 CASE PRESENTATION

A 35-year-old married, Asian male, presented in the clinical set-up with headache, neck pain, and fluctuating fever for 4 days before admission. The patient experienced intermittent seizures, was then hospitalized, and continued with anti-tuberculosis drugs. The patient had a history of hospitalization due to TBM with hydrocephalus 1 month prior to admission. The neurologist observed that the patient looked thin and malnourished and consulted the patient with the clinical nutrition department. On the 6th day after admission, the patient was assessed and diagnosed with severe malnutrition with decreased food intake, decreased body weight, muscle and fat wasting, and decreased functional capacity (Table 1). The

patient showed no sign of dysphagia, so it was not suggested to use a nasal feeding tube (NGT). Other clinical features can be seen in Table 2. The nutritional intake history was obtained using FFQ (Food Frequency Questionnaire) and 24H dietary recall and showed a decrease in energy (Figure 1) and an increase after initial assessment and nutritional suggestion. On the 16th–18th day, the diet was changed to a liquid meal via NGT due to the disability to swallow and seizure due to hydrocephalus (based on a CT scan) and the patient underwent VP Shunt Repair. There was no body weight change in the patient during observation, and the functional capacity that was assessed using a hand dynamometer and Barthel index was increased (Table 3).

Table 1. Patient characteristics.

Gender	Male
Age (year)	35
Diagnosis	Meningitis Tuberculosis on anti-tuberculosis drugs with hydrocephalus post-VP shunt
Medical Nutrition Diagnosis	Severe malnutrition, cachexia
Length of stay	26 days
BW at administration (kg)	43
BW at discharge (kg)	43
BMI	14,5
Comorbidity	–
Clinical Outcome	Functional capacity improvement. Discharged with NGT

Notes: NGT = Nasogastric-tube; BW = Body weight; BMI = Body mass index

Table 2. Clinical features and physical examination of the patient.

Chief complaint	Seizure and loss of consciousness
Symptoms	<ul style="list-style-type: none"> ○ headache and stiff neck ○ slumber ○ weakness ○ seizure ○ slumber ○ decrease in physical abilities
Close contact with pulmonary TB patients	–
Comorbidity	–
Intake decrease	+
Body weight loss	+, 19% in 6 months
Consciousness	Somnolent
Stiff neck	–
Seizures	+
Cranial Nerves Paresis	–
Dysphagia	–
NGT	–
Fat loss	+
Muscle loss	+
Edema	–

On the 24th day, the consciousness increased, eyes opened spontaneously and limbs moved slowly. Energy intake data was obtained using 24H dietary recall (Figure 2). Protein and total lymphocyte count (TLC) during hospitalization were observed and presented in Figures 3 and 4. On the last day of hospitalization, the patient still felt dizzy, and can

swallow small pieces of food. The meal during hospitalization was 1 kcal/mL liquid blenderized meal, 13% protein, 23% fat, and 55% carbohydrate with an oral trial, and swallowed without choking. We planned to keep the NGT and the family was informed to give protein energy-dense liquid food at home and oral training. The patient was suggested to have a week of 6 times liquid meals a day with a total of 1700 kcal per day (40 kcal/kgBW) and 19% protein, consisting of 3 times of blenderized meals (mixture of home-made high protein milk, white egg, and coconut oil) and 3 times liquid snack (fruit juice).

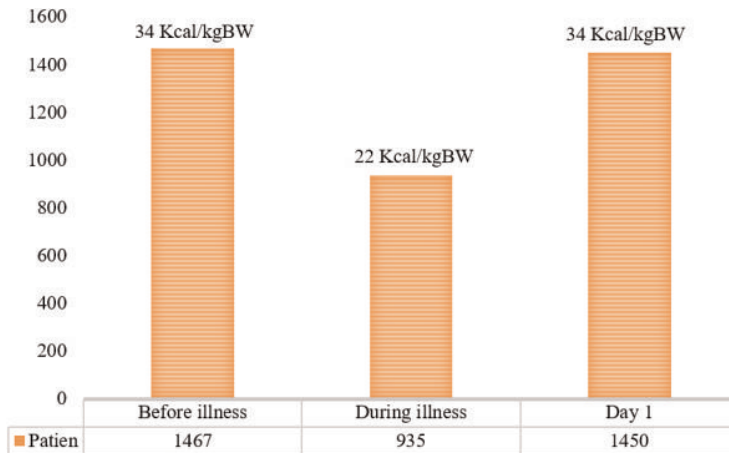


Figure 1. Energy Intake before, during illness, and day 1 of nutritional assessment.

Table 3. Patient's functional capacity.

	Score
Barthel Index 0 (day 6th)	0 (zero)
Barthel Index 1 (day 26th)	6 (six)
HGS 0 (day 8th; dominant hand)	R: 13,4 kg
HGS 1 (day 26th; dominant hand)	R: 18,8 kg

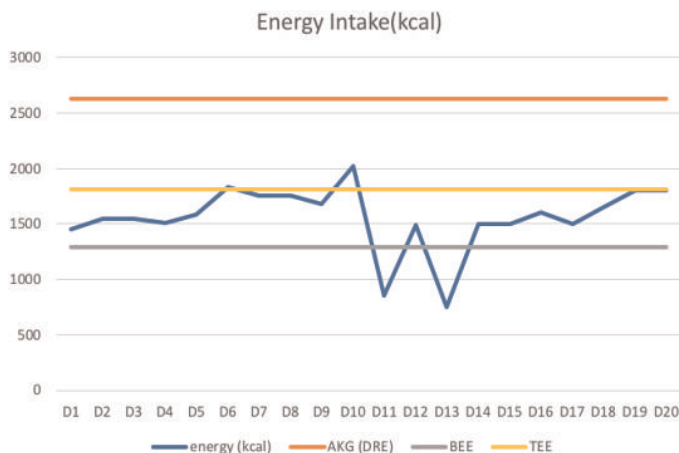


Figure 2. Energy intake during hospitalization.

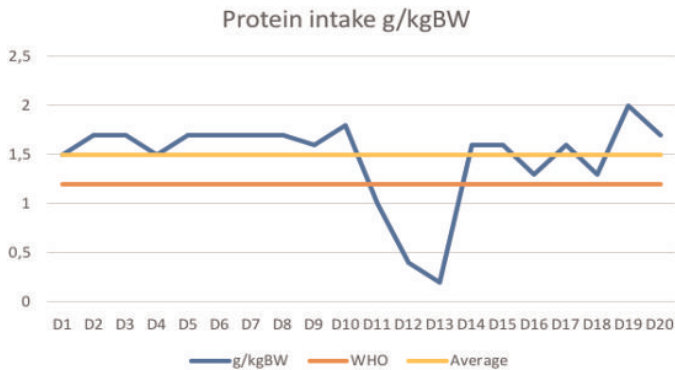


Figure 3. Protein intake during hospitalization.

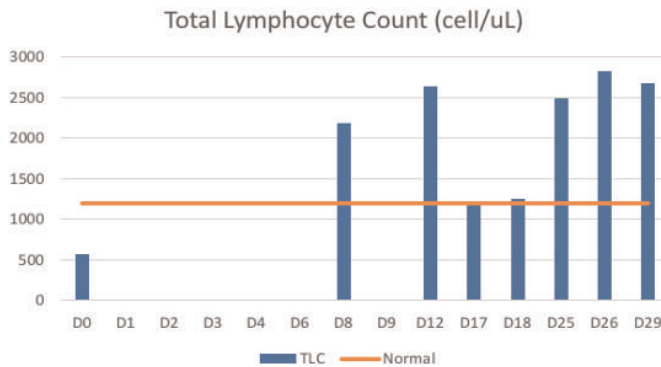


Figure 4. Total lymphocyte count.

3 DISCUSSION

TBM is an extrapulmonary disease of TB infection, with malnutrition as a comorbidity, and further affecting the immune system (Imran *et al.* 2018; Kumar *et al.* 2016; Thwaites *et al.* 2002; World Health Organization 2016). The initial signs of TBM are fever and headache, then progressing to neurological deficits and dysphagia (Tan *et al.* 2017), which further develop malnutrition and cachexia which can cause high mortality due to wasting syndrome, and metabolic changes (Gupta *et al.* 2009; Karyadi *et al.* 2000). Patient in this observation showed the wasting syndrome as the result of metabolic changes during infection courses. Malnutrition was diagnosed based on physical examination, and food intake decreased due to appetite loss, consciousness loss, and other neurologic deficits that caused problems in chewing and swallowing function (Casanas *et al.* 2017; Thwaites & Hien 2005; Kelly & Buchholz 1996; Macallan 1999; Misra *et al.* 2011). Malnutrition screening tools (MST) can be used to assess the malnutrition risk of the hospitalized patient based on the weight loss, intake decrease or appetite loss, and other medical conditions that affect those first two conditions. According to Leandro-Merhi *et al.* (2015), most of the malnutrition in patients appears in the first week of hospitalization and affects the clinical outcome of the treatment, length of stay, and hospitalization cost. Thus, high-risk patients are advised to undergo nutritional management from the first week of treatment or when screening results indicate a high risk of malnutrition.

Decreased appetite occurs in pulmonary TB patients due to an inflammatory process that affects the regulation of hunger-satiety in the hypothalamus and endocrine regulation associated with hunger (insulin, leptin), which is assumed to appear as well in TBM patients (Mak *et al.* 2006). Nutritional status of the patient is assessed using BMI WHO criteria and ASPEN criteria (Menteri Kesehatan Republik Indonesia 2019; White *et al.* 2017; World Health Organization 1999).

Based on the ASPEN (White *et al.* 2017), adult malnutrition was assessed by disease course length, history of low energy intake, weight loss, and physical characteristics. The patient showed an intake decrease which is only 900s kcal while the intake before illness was 1400s kcal on average (64% of than usual intake) and there was 19% body weight loss in less than 6 months. On physical exams, the patient showed a decrease in fat mass from sunken periorbita and prominent rib cage, decreased muscle mass from the concave temples, and muscle wasting in the extremities. Objectively, the grip strength and the Barthel Index were decreased in this patient indicating dependency. In addition to the ASPEN criteria, edema was not present in patient assessment which could be due to the decrease of plasma albumin synthesis in hepatocytes (Menteri Kesehatan Republik Indonesia 2019).

Barthel index (BI) score can be used to assess the therapeutic outcome of TBM patients (Mahoney & Barthel 1965), which consists of bowel control and micturition components, tidiness and personal hygiene (hygiene), clothing, use of toilets/defecation, moving positions/locations, and eating. In this patient, the initial BI score was zero, but at the end of hospital treatment (day 26) the BI score was six, which came from: 1) clothing with little help; 2) moving position where the patient can move into sitting position with just one helper; and 3) patient can control his defecation. On day 8 of hospitalization (initial nutritional assessment), the score of the Hand Grip assessment was 13,4 kg, and on day 26, there was an increase to 18.8 kg. The increase in hand grip could be due to an increase in energy and protein intake, which have an effect on increasing muscle strength, a physiological effect on the central nervous system, and an increase in appetite (Cangiano *et al.* 1996).

Dysphagia occurs in 42% to 67% of stroke patients, as well as in TBM patients with stroke symptoms, and affects nutritional intake due to the risk of aspiration (Perry & Love 2001; Tan *et al.* 2017). NGT use can be considered or follow the dietary consistency recommendations for dysphagia patients (Kim & Byeon 2014; Trapl *et al.* 2007).

According to WHO recommendations, a pulmonary TB patient's energy requirement is 40 kcal/kgBW (World Health Organization 2013). In patients with neurological problems, the European Society of Parenteral and Enteral Nutrition (ESPEN) recommends 20–30 kcal/kgBW (Breton 2016; Burgos *et al.* 2018). The recommendation of the Indonesian Ministry of Health in PNPk Adult Malnutrition for patients with active pulmonary TB is 35–40 kcal/kgBW (Menteri Kesehatan Republik Indonesia 2019). In this patient, there is no noticed history of TB infection, but based on assessment, the patient is classified into severe malnutrition, so we plan about 40 kcal/kgBW with high protein intake. However, the patient also had a very high risk of refeeding syndrome based on the history of starvation, BMI 14,5 kg/m² and sign of fat and muscle wasting. Based on patient intake analysis, the initial energy intake was 1450 kcal (34 kcal/kgBW), with 1,5 g/kgBW of protein. Increase of energy and protein intake was gradually into calorie intake target and protein of 2 g/kgBW. Examination of serum potassium, magnesium, and phosphate levels was ordered to observe the refeeding syndrome.

On day 10, the patient had reached more than the targeted energy intake and protein intake reached 1,8 g/kgBW. Energy and protein intake give support to the patient's immune system and that can be seen from the patient's TLC increase above 2000 cells/uL. That condition was also shown by Gunarsa *et al.* (2011), which concluded that nutrition status correlates with total lymphocyte count. (Allende *et al.* 1998; Komaki *et al.* 1997). In this patient, there is increment in TLC from 570s cells/uL to 2000s cells/uL in 8 days after nutritional management, which can be assumed that nutritional intervention with high protein affects patient's biochemistry parameter.

The patient lost his ability to eat in 2nd week, then applied NGT and IV route parenteral nutrition, underwent VP shunt repair, and was admitted to the intensive care unit. The TLC was decreasing but still maintained above the reference number (1200 cells/uL) but increased on day 25 (2500 cells/uL). On the 26th day, the patient was discharged from the hospital as the functional capacity and eating ability was increased. The patient's body weight is 43 kg, the same as BW at the first nutritional assessment. This condition was assumed that the patient body mass was maintained within 3 weeks of observation as a result of high protein during hospitalization. A nasogastric tube was still administered while the oral intake was tested on the patient. The patient is still given liquid enteral food that is administered via NGT and oral intake has still been tried. The patient went home with silicon NGT applied, the patient's family was educated to make liquid enteral food at home and would be visited 3 times at the home care setting. Home nutrition advice is based on the patient's ability to eat orally and the patient's tolerance to liquid food on the last day of hospitalization. For the home care setting, the energy was planned based on the guideline from the Indonesian Ministry of Health for Adult Malnutrition with TB infection (40 kcal/kgBW) and protein recommendation 1,5-2 g/kgBW (20%). However, due to economic conditions, the patient and family cannot fulfill the protein requirement (20%), so we gave the patient 17% of protein which fulfills the requirement as 1,5g/kgBW.

CONFLICT OF INTEREST

There is no conflict of interest in this case report

ACKNOWLEDGEMENT

The authors express their thanks to dr. Darma Imran, Sp.S(K), and dr. Kartika Maharani, Sp.S, as lecturing physician in the Neurology Department FKUI-RSCM, dr. Ahdinar as a Neurology Resident, and the nurses at the Neurology Ward of Building A of RSCM in Jakarta

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Neutrophil-to-lymphocyte ratio is associated with Mid-Term BPV in hypertensive COVID-19 patients

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ABSTRACT: Neutrophil-to-lymphocyte (NLR) is an inexpensive and feasible inflammatory marker. Inflammation is crucial in the pathogenesis and progression of COVID-19 with hypertension. Blood pressure control in hypertension is influenced by blood pressure variability. 192 COVID-19 patients with hypertension who were administered to Sebelas Maret University Hospital from June 2020 to February 2022 were included in this observational analytical study with a cross-sectional approach. Data were analyzed using Spearman or Pearson correlation analysis. Comparative analysis of independent T-test or Mann Whitney was used on numerical variables and Chi-Square test on categorical variables. There was a positive (unidirectional) and significant correlation ($r = 0,223$, $p = 0,002$) between the NLR dan blood pressure variability in COVID-19 patients with hypertension at Sebelas Maret University Hospital. There was a significant difference in the variables of admission oxygen saturation $<93\%$ ($p < 0.001$) and mortality ($p < 0.001$), which were found to be higher in patients with high NLR levels (≥ 5.8) than normal NLR levels (< 5.8). This study showed that admission NLR was weakly and positively correlated with blood pressure variability in COVID-19 patients with hypertension at Sebelas Maret University Hospital. An increase in admission NLR above the normal upper limit, can elevate the blood pressure variability. Therefore, it needs to be considered.

1 INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). The virus was first identified in Wuhan, China, on January 7, 2020. On March 11, 2020, the World Health Organization (WHO) announced the case of COVID-19, which had spread to 114 countries as a global pandemic (World Health Organization, 2020). Transmission of COVID-19 is effortless from person to person, one of which is through a splash of saliva (Parasher 2021). As of December 29, 2021, Indonesia was ranked 14th with the most accumulation of positive confirmed cases in the world, namely 4,262,351 cases with 144,081 deaths. COVID-19 cases in patients with comorbidities have a higher mortality rate than patients without comorbidities (Du *et al.* 2020). The most common comorbidities in COVID-19 patients are hypertension and diabetes mellitus (Sanyaolu *et al.* 2020).

Hypertension is associated with a high risk of cardiovascular disease events and target organ damage. Optimal blood pressure control can prevent worsening clinical outcomes of COVID-19 patients with comorbid of hypertension (Ran *et al.* 2020; Sheppard *et al.* 2021). Blood pressure control is affected by changes in blood pressure or usually named blood pressure variability (BPV) (Wei-jie Guan *et al.* 2020) (Li *et al.* 2021). BPV can be differentiated based on measurement intervals, namely in the short-term (over 24 hours or beat by beat), mid-term (day-by-day), and long-term (visit-to-visit) (Parati *et al.* 2013). In their research stated that high BPV in the mid-term (day-by-day) is associated with worsening the clinical condition of COVID-19 patients (Sheppard *et al.* 2021). This is caused by systemic inflammatory events that will disrupt blood pressure regulation by the endothelium's nitric oxide production. At the same time, nitric oxide regulates aortic stiffness, a significant blood pressure determinant, thereby increasing BPV (Amar *et al.* 2021; Sheppard *et al.* 2021). This systemic inflammation is caused by a hyperinflammatory response to the SARS-CoV-2 virus, which enters cells in the lungs via the angiotensin-converting enzyme 2 (ACE2) receptor, and it also explains the correlation between hypertension and COVID-19 (Zhou *et al.* 2020).

The role of inflammatory markers is quite significant in assessing the course of COVID-19 disease, one of which is the neutrophil-to-lymphocyte ratio (NLR). NLR is an inexpensive and feasible inflammatory marker of a systemic inflammatory response. From the complete blood count, the absolute neutrophil count divided by the absolute lymphocyte section, an elevated NLR indicates the presence of an inflammatory response lesion and can be a marker of disease severity (Song *et al.* 2021). NLR was reported to be increased in non-dipper hypertensive patients than in dipper and normotensive patients. NLR could independently predict short-term BPV (Kiliçaslan *et al.* 2015). In contrast, Gang & Yanyan (2016) found that there was no difference in NLR in hypertensive and normotensive patients (Gang & Yanyan 2016). (Magdás *et al.* 2020), in their research said short-term BPV (24 hours), which is calculated as Average Real Variability (ARV), positively correlated with NLR and red blood cell distribution width (RDW) (Magdás *et al.* 2020).

However, information on the relationship between mid-term (day-by-day) BPV and NLR inflammatory factors, especially in COVID-19 patients with hypertension, is still lacking. Therefore, this study was conducted to help provide information and reference regarding the relationship between NLR and mid-term blood pressure variability in COVID-19 patients with hypertension.

2 METHODS

2.1 Study design and population

This research is analytical and observational with a cross-sectional approach. The research data were obtained from medical records. The population is COVID-19 patients with comorbid hypertension at Sebelas Maret University Hospital in June 2020-February 2022. Inclusion criteria include: 1) COVID-19 patients based on RT-PCR examination; 2) have a history of diagnosis of hypertension or who are taking or have ever taken antihypertensive drugs; 3) have NLR results and blood pressure measurement results within five days of admission. Meanwhile, the exclusion criteria included hematological disorders, autoimmune diseases, cancer, and pregnant patients. The sampling technique used is total population sampling. This study obtained 226 samples, but only 192 patients met the inclusion criteria. This research has been approved by the Ethics Commission of RSUD Dr. Moewardi Number 514/IV/HREC/2022.

2.2 Blood pressure measurement

The blood pressure measurement was used five days after admission, measured twice daily, in the morning and evening. The indicator of blood pressure variability in this study is illustrated by the calculation of the standard deviation (SD) and the coefficient of variation (CV) of systolic and diastolic blood pressure.

2.3 Statistical analysis

To compare baseline characteristics, we divided participants into two groups based on NLR levels: <5.8 (normal) and ≥5.8 (high). To compare the difference between the two groups, if the numerical data were normally distributed and homogeneous, the unpaired t-test was used; if not, then the Mann-Whitney test was used. An analysis of variables with categorical data was performed using the Chi-Square test. Pearson analysis or Spearman is used to examine the relationship between NLR and BPV. All statistical analyzes were performed using the SPSS version 26 application.

3 RESULTS

3.1 Baseline characteristics of COVID-19 patients with hypertension

Table 1 shows that the mean age of the patients in this study was 55.70 years. A total of 101 (52.7%) patients were male. Most of the patients (72.4%) had oxygen saturation levels ≥93% at admission, whereas 72 (37.5%) patients had oxygen saturation <93%. There were 128 (66.7%) patients with comorbidities other than hypertension, in which diabetes mellitus (40.6%) was the most common comorbid. The median length of stay of patients in this study was 11 days. A total of 36 patients (18.8%) died. Table 1 also shows a comparative analysis of each variable on NLR levels. In that analysis, between-group comparisons showed significant differences in oxygen saturation at admission (p<0.001) and patient outcome (p<0.001). Meanwhile, there were no significant differences in age, sex, comorbidities, and length of stay variables.

Table 1. Clinical characteristics of COVID-19 patients with hypertension.

Variable	Total (n = 192)	NLR		P value
		Normal (n = 116)	High (n = 76)	
Age (year), (mean±SD)	55,70 ± 12,37	54,70 ± 13,02	57,24 ± 11,21	0,165 ^a
Gender (n (%))				0,878 ^b
Male	101 (52,6%)	60 (51,7%)	41 (53,9%)	
Female	91 (47,4%)	56 (48,3%)	35 (46,1%)	
Admission O2 saturation, (n (%))				<0,001 ^{b*}
≥93	120 (62,5 %)	87 (75%)	33 (43,4%)	
<93	72 (37,5%)	29 (25%)	43 (56,6%)	
Other comorbid (n (%))				-
Diabetes melitus	78 (40,6%)	39 (20,3%)	39 (20,3%)	
Impaired kidney function	38 (19,8%)	15 (7,81%)	23 (11,98%)	
Heart disease	67 (34,9%)	41 (21,35%)	26 (13,54%)	
Dyslipidemia	6 (3,1%)	4 (2,06%)	2 (1,03%)	
Asthma	2 (1%)	2 (1%)	0 (0%)	
Bronchitis	3 (1,6%)	2 (1,06%)	1 (0,53%)	
Cerebrovascular disease	2 (1%)	2 (1%)	0 (0%)	
No other comorbid	64 (33,3%)	47 (24,45%)	17 (8,84%)	
Number of Comorbid				0,123 ^b
1 Comorbid	137 (71,3%)	88 (75,8%)	49 (64,5%)	
>1 Comorbid	55 (28,7%)	28 (24,2%)	27 (35,5%)	
Length of Stay (days)	11 (5–33)	11 (5–31)	11 (5–33)	0,717 ^c
Patient output				<0,001 ^{b*}
Live	156 (81,3%)	109 (93,9%)	47 (61,8%)	
Death	36 (18,8%)	7 (6.1%)	29 (38,2%)	

Abbreviations: ^a T-Test; ^b Chi Square; ^c Mann-Whitney; *significant p<0,05

3.2 Overview of NLR

The NLR level of 192 COVID-19 patients with hypertension treated at Sebelas Maret University Hospital was 6.17, with an average of neutrophil 73.04% and 18.21% of lymphocytes.

3.3 Comparison of blood pressure variability

The absolute value, SD, and CV of blood pressure are shown in Table 2. There were differences in the mean SD SBP ($p = 0.005$), SD DBP ($p = 0.049$), and CV SBP ($p = 0.028$) in patients with normal NLR levels (<5.8) and high NLR levels (≥ 5.8).

Table 2. Comparison of blood pressure variability in COVID-19 patients with normal and high NLR.

Variable	Total (n = 192)	NLR		P values
		Normal (n = 116)	High (n = 76)	
SBP (mmHg)	139,76 ± 13,18	138,18 ± 14,19	141,98 ± 13,30	0,058 ^a
DBP (mmHg)	82,67 ± 8,93	82,27 ± 8,49	83,02 ± 9,12	0,662 ^a
Systolic Variability				
SD SBP (mmHg)	16,17 (5,85–36,02)	15,44 (5,85–32,66)	17,24 (8,76–36,02)	0,006^c*
CV SBP (%)	12,12 ± 3,81	11,33 ± 3,58	12,86 ± 3,49	0,028^a*
Diastolic Variability				
CV DBP (%)	12,26 (3,71–35,67)	11,88 (3,71–35,67)	12,89 (5,13–32,19)	0,085 ^c
SD DBP (mmHg)	9,88 (3,24–30,32)	9,60 (3,24–30,32)	10,41 (4,19–24,88)	0,049^c*

Abbreviations: SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; BP, Blood Pressure; SD, Standard Deviation; CV, Coefficient of Variation; ^a T-Test; ^c Mann-Whitney; *significant $p < 0,05$

3.4 Relationship between NLR and BPV in COVID-19 patients with hypertension

Table 3 shows a significant correlation ($p < 0.05$) in SBP ($p = 0.023$) and an indicator of blood pressure variability in the form of SD SBP ($p = 0.002$) with NLR levels. SBP has a correlation coefficient (r) of 0.164, thus illustrating a very weak and significant unidirectional relationship between systolic blood pressure and NLR levels. In addition, SD SBP has a correlation coefficient (r) of 0.223. It illustrates a weak but statistically significant unidirectional relationship between systolic blood pressure variability and NLR levels in COVID-19 hypertensive patients at Sebelas Maret University Hospital.

Table 3. NLR correlation test with blood pressure variability.

	NLR		
	r	P	N
SBP	0,164	0,023*	192
DBP	0,053	0,464	192
Systolic Variability			
SD SBP	0,223	0,002*	192
CV SBP	0,109	0,132	192
Diastolic Variability			
CV DBP	0,128	0,078	192
SD DBP	0,141	0,051	192

Abbreviations: r, coefficient correlation; p, significance; N, total data

4 DISCUSSION

4.1 Baseline characteristics of hypertensive COVID-19 with NLR

In COVID-19 patients, the occurrence of a viral infection can tend to cause oxygen circulation to be disrupted because fluid buildup occurs in the lung parenchyma (Shenoy *et al.* 2020). Research conducted by Moradi *et al.* (2021) on COVID-19 patients at Imam Reza Hospital, Iran, stated that 142 patients with oxygen saturation $<90\%$ had higher NLR compared to 77 patients with oxygen saturation $\geq 90\%$ ($p = 0.008$) (Moradi *et al.* 2021). Although using a different oxygen saturation cut-off, this study aligns with these studies. In addition, Halil *et al.* (2022), in their study showed that the group of patients with severe severity (oxygen saturation $<93\%$) had a statistically significantly higher NLR than the group with mild-moderate severity ($p < 0.01$) (Halil *et al.* 2022). Oxygen saturation $<93\%$ is one of the criteria for a severe degree of COVID-19. This is in line with the study of Liu *et al.* (2020) that NLR levels are related to the degree of severity of COVID-19 (Sheppard *et al.* 2021). Older age is also associated with the severity of COVID-19 and mortality; this is associated with a faster inflammatory process and decreased immunity (Du *et al.* 2020). The mean age in this study was 55.7 years, which is lower than the study by Nam *et al.* (2021), 70 years and X. Zhou *et al.* (2020), 64.8 years (Nam *et al.* 2021; Zhou *et al.* 2020). In this study, more patients were male (52.6%). Gender can affect the susceptibility to COVID-19, according to previous research, because men have more ACE2 expression in circulation and lungs than women, and circulation and lungs are the main routes of SARS-CoV-2 transmission (Naaraayan *et al.* 2020). Although in re-search, this is in line with the theory, where patients with high NLR levels have an older average age and are dominated by males than females. Still, the two groups have no significant difference regarding age characteristics ($p = 0.165$) and sex ($p = 0.878$).

A study conducted in China showed that 50% of patients hospitalized in Hubei Province had comorbidities (Guan *et al.* 2020a, 2020b). In this study, the most common comorbid besides hypertension was diabetes mellitus (40.6%), with a median length of stay of 11 days. This is in line with the study of X. Zhou *et al.* (2020), where the other comorbidity that most COVID-19 patients with hypertension have is diabetes mellitus (25%), and the length of stay is 11.1 days (Zhou *et al.* 2020). This study, however, found no statistically significant differences in the types of comorbidities, the number of comorbidities, and the length of stay between the two groups. The theory of the process of immune system dysregulation by blood pressure can explained the relationship between comorbid hypertension and COVID-19.

High NLR levels associated with mortality in hospital COVID-19 patients have been widely known and reported (Du *et al.* 2020; Pertiwi *et al.* 2022). The results of this study are consistent with these studies, where there was a significant difference in patient outcomes between the two groups ($p < 0.001$). In a study conducted by Çimen *et al.* (2017), there was no significant difference in SBP ($p = 0.09$), SD SBP ($p = 0.170$), and SD DBP (0.374) on NLR levels, while DBP had significant results with a value of $p = 0.003$. In addition, there were also morning SBP ($p = 0.048$) and evening DBP ($p = 0.001$), which were significant (Cimen *et al.* 2017). There were several differences, this could be because the study by Çimen *et al.* (2017) used only a population of hypertensive patients with-out being infected with COVID-19, which were then grouped into quartiles based on NLR level. In addition, the measurement of BPV is only carried out in a short period using the ABPM method. Meanwhile, this study used a population of COVID-19 patients with hypertension who used the NLR cut-off based on EWS; then, BPV was measured in the mid-term for five days. In this study, SD SBP ($p = 0.006$), SD DBP ($p = 0.049$), and CV SBP ($p = 0.028$) were significantly different among patients with normal (<5.8) and high (≥ 5.8) NLR levels. This study's systolic and diastolic blood pressure co-efficient variation is $>11\%$. Juhanoja *et al.* (2017) find this is associated with a higher risk of cardio-vascular disease in Europe and Asia (Juhanoja *et al.* 2017).

4.2 NLR with blood pressure variability

The results of this study showed that the average NLR level of 192 COVID-19 patients with hyper-tension treated at Sebelas Maret University Hospital was 6.17, whereas the normal level of NLR based on the Early Warning Score (EWS) was <5.8 . The average NLR in this study was higher than the study conducted by Amar *et al.* (2021), whose average NLR was 5.57 (Amar *et al.* 2021). There were 76 patients (39%) with elevated NLR levels above normal. This is in line with the theoretical basis where SARS-CoV-2 infection will cause systemic inflammation, which triggers the release of pro-inflammatory signals resulting in a cytokine storm. These cytokines include IL-8, which functions for neutrophil degranulation and mitosis, so if IL-8 is up-regulated in SARS-CoV-2 infection, neutrophils will also increase. The increase in neutrophils and decrease in lymphocytes in COVID-19 will cause a high NLR. This was also in accordance with this study, where there was an increase in neutrophils with an average of 73.04% (normal: 50–70%), while there was a decrease in lymphocytes with an average of 18.21% (normal: 22–44%). In addition, neutrophils secrete mediators responsible for the inflammatory response so that they can cause tissue damage, disrupt plaque, trigger oxidative stress, and further increase the risk of hypertension (Liu *et al.* 2015). Table 2 shows a weak and significant unidirectional relationship between NLR levels and SBP ($p = 0.023$; $r = 0.164$) and SD SBP ($p = 0.002$; $r = 0.223$) in COVID-19 patients with hypertension at Sebelas Maret University Hospital. The results of this study may differ from several similar studies. A weak and significant unidirectional relationship between NLR and BPV was also found in the study of Magdás *et al.* (2020) ($p = 0.05$; $r = 0.07$) (Magdás *et al.* 2020). This study used 53 hypertensive patients at Mures Hospital whose blood pressure was measured ABPM, and BPV was calculated using the ARV formula. Increased BPV is related to the level of inflammation, such as NLR, but in that study it was also concluded that other indicators are related to increased BPV, namely in the form of RDW.

Kiliçaslan *et al.* (2015) showed a weak and significant inverse relationship ($r = -0.246$; $p = 0.003$) between NLR and BPV for 24 hours (Kiliçaslan *et al.* 2015). The study differed in that it used data from hypertensive and normotensive patients at Tepecik Research Hospital, which were divided in-to four groups. NLR increased in non-dipper hypertensive patients when compared with dipper and normotensive subjects. NLR was significantly correlated with SBP ($p = 0.031$; $r = 0.031$) and DBP ($p = 0.032$; $r = 0.176$) at night, as well as BPV, which was calculated by the formula $100 \times [1 - (\text{sleep systolic blood pressure} / \text{awake systolic blood pressure})]$. Measuring dipper and non-dipper blood pressure in hypertensive patients using ABPM in 24 hours can be one of the reasons for the negative correlation coefficient. This could be since 24-hour blood pressure follows the body's circadian rhythm. Because blood pressure is higher during the day than at night, so if BPV decreases $<10\%$ (non-dipper), it is closely related to an increased risk of cardiovascular disease, one of which is characterized by increased NLR. A similar study was also studied by Yıldırım *et al.* (2019), where NLR had a significant relationship with BPV between morning and night ($p < 0.01$; $r = -0.188$), night SBP ($p = 0.003$; $r = 0.141$), and night DBP ($p = 0.020$; $r = 0.113$) (YILDIRIM *et al.* 2019).

This research has been carried out optimally, but there are still limitations. This study used a cross-sectional observational design at one hospital and in several studies carried out standardized measurements using the same person and method of measurement, whereas this study was limited because it used medical record data. For further research, larger and multicentric samples can be used with primary data so that analysis can be carried out with more comprehensive data on basic characteristics, physical examination, and laboratories in COVID-19 patients.

5 CONCLUSION

This study showed a significant relationship between the value of the NLR and BPV in COVID-19 patients with comorbid hypertension, where a positive correlation was obtained.

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Prospects of melatonin as an adjuvant therapy in schizophrenic patients: A bibliometric analysis

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ABSTRACT: Adjuvant therapy using antioxidants or anti-inflammatories still provides varied outcomes in schizophrenic patients. The debated one recently is melatonin. This study investigated the prospects of melatonin as an adjuvant therapy in schizophrenic patients. The study was conducted with bibliometric analysis visualization using VOSviewer. The data were articles taken from the Scopus database between 2003–2022. The bibliometric analysis focused on the co-occurrence of the keywords of these articles, especially melatonin, adjuvant therapy, and schizophrenia. The VOSviewer visualization showed that out of 460 Scopus-indexed articles, ten research clusters related to adjuvant therapy in schizophrenia were obtained. The visualization results also revealed that study on melatonin as an adjuvant therapy in schizophrenia is still scarce. This study concluded that using melatonin as an adjuvant therapy in schizophrenic patients is still prospective to be developed.

1 INTRODUCTION

Schizophrenia is a severe mental disorder with positive and negative symptoms, cognitive impairment, and behavioral disorder, and it significantly impacts public health (Stepnicki *et al.* 2018). The incidence of schizophrenia is reported between 8 and 43 per 100,000 individuals (Orrico-Sánchez *et al.* 2020) 20–30% of individuals with schizophrenia do not respond to first-line therapy and do not achieve a condition of remission (Zipursky 2014). Patient adherence to treatment and resistance to drugs also result in the success of schizophrenia management being suboptimal (Harrison *et al.* 2021) Therefore, additional treatment strategies are now being developed. One is administering adjuvant therapy to improve the response to schizophrenia therapy (Tseng *et al.* 2016).

Adjuvant therapy is defined as therapy given concurrently with the primary therapy intending to improve clinical symptoms and the occurrence of relapses. Allopurinol as an adjuvant therapy may provide advantages in schizophrenic patients who are less responsive to treatment (Buie *et al.* 2006). Nutritional interventions through supplementation, such as vitamin B9 (*I-methylfolate*), also showed improvement in negative symptoms of schizophrenic patients. Anticonvulsants, valproic acid, can also be used as adjuvant therapy in treatment-resistant schizophrenia (Anderson & Maes 2012; Tseng *et al.* 2016) Some studies have reported that the effects of adjuvant therapies vary on schizophrenic patients (Patel

et al. 2014) One hypothesis states that the neuroimmune system plays a role in various psychiatric disorders, including schizophrenia (Murphy *et al.* 2021) Melatonin can weaken pro-inflammatory cytokines and other inflammatory mediators and act as a free radical scavenger that protects from oxidative damage (Anderson & Maes 2012; Tseng *et al.* 2016) Melatonin is expected to become an adjuvant therapy to improve the clinical symptoms of schizophrenia through inflammatory pathways.

As the use of adjuvant therapies increases in managing schizophrenia, thus we conducted a bibliometric study to investigate the prospect of melatonin as an adjuvant therapy. This study uses a bibliometrics visualization approach to make it easier to conclude the research objectives. Bibliometrics is a quantitative study that analyzes the social and structural relationship among topics, thus allowing researchers to easily acquired a study depiction, identify study gaps, find new ideas, and determine the position of our contribution to a study topic (Donthu *et al.* 2021).

2 METHODS

The steps used in this study were based on the four stages formulated by Donthu *et al.* (2021). First, determine the purpose and scope of the study. This study focused on pinpointing the position of melatonin at a specific period as adjuvant therapy in schizophrenic patients. This study covered 20 years between 2003 and 2022. Second, determine the technique of bibliometric analysis. Since this study aimed to see an overview of the research topic in a certain period, the method used co-occurrence analysis on author keywords. Third, data collection. We limited the data used for this analysis to using only Scopus databases. Fourth, conduct a bibliometric analysis. The bibliometric analysis we use is science mapping because it is easier to find research gaps in large amounts of datasets.

In analyzing the data obtained from Scopus, we used VOSviewer because this application highlighted the ease of reading graphs and interpreting bibliometric data processing results (van Eck & Waltman 2010). The data is analyzed with VOSviewer software which can easily analyze data from the Scopus database (Manoj Kumar *et al.* 2022). This ease was reaffirmed by Cobo *et al.* (2011), where it is said that VOSviewer pays special attention to graphic representation. Visualization makes it easier to interpret large numbers of data.

This study focused on finding topics rarely studied in a particular field using bibliometrics analysis. Bibliometrics study identifies emerging topics, declining topics, and study topic gaps (Obidat 2022; Umeokafor *et al.* 2022). This identification was made with co-occurrence analysis on keywords. Previous medical studies using co-occurrence analysis with VOSviewer were delivered by Gautam (2019) and Andersen *et al.* (2020).

3 RESULTS AND DISCUSSION

This study's data was taken from the Scopus database on October 20, 2022. The queries used are limited so that they only meet the criteria: Adjuvant therapy and schizophrenia keywords, period of 2003–2022, English articles, and not distinguishing whether they are published as journal articles or reviews. The selected keywords are still general to capture as much of the initial data used for subsequent analysis as possible. The query generated 460 documents and was exported into CSV format. The complete query is as follows:

```
(TITLE-ABS-KEY ("adjuvant therapy" AND schizophrenia) AND (LIMIT-TO (PUBYEAR, 2022) OR LIMIT-TO (PUBYEAR, 2021) OR LIMIT-TO (PUBYEAR, 2020) OR LIMIT-TO (PUBYEAR, 2019) OR LIMIT-TO (PUBYEAR, 2018) OR LIMIT-TO (PUBYEAR, 2017) OR LIMIT-TO (PUBYEAR, 2016) OR LIMIT-TO (PUBYEAR, 2015) OR LIMIT-TO (PUBYEAR, 2014) OR LIMIT-TO (PUBYEAR, 2013) OR LIMIT-TO
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(PUBYEAR, 2013) OR LIMIT-TO (PUBYEAR, 2012) OR LIMIT-TO (PUBYEAR, 2011) OR LIMIT-TO (PUBYEAR, 2010) OR LIMIT-TO (PUBYEAR, 2009) OR LIMIT-TO (PUBYEAR, 2008) OR LIMIT-TO (PUBYEAR, 2007) OR LIMIT-TO (PUBYEAR, 2006) OR LIMIT-TO (PUBYEAR, 2005) OR LIMIT-TO (PUBYEAR, 2004) OR LIMIT-TO (PUBYEAR, 2003) AND (LIMIT-TO (LANGUAGE, "English"))

For ease of analysis, the previous query is hereinafter referred to as Query 1. To perform the visualization, the software used is VOSviewer version 1.6.18, which was launched on January 24, 2022. The step taken for this visualization is, first, choosing to create a map based on bibliographic data because we will focus on the co-occurrence of the keywords only. Second, choose a data source from Scopus with the CSV extension already saved in the previous step. Third, select the type of co-occurrence analysis and the unit analysis author keyword. In this step, we also created a thesaurus so that keywords that are commensurate with their meaning can be combined to accumulate. Fourth, it provides a minimum occurrence threshold of keywords. We chose the minimum number of occurrences of 4 because the keyword melatonin has yet to appear on the visualization at larger values. In this value, only a total of 78 keywords meet the threshold from the 918 keywords. After visualization, it can be seen that the Scopus data forms 10 clusters. Among the 78 keywords visualized, 4 of them have more than 20 occurrences, namely schizophrenia (209 times), antipsychotic (53 times), negative symptom (24 times), and bipolar disorder (21 times). Next, we analyzed 2 clusters: A cluster in which keywords are connected to melatonin and a cluster in which keywords are connected to adjuvant therapy.

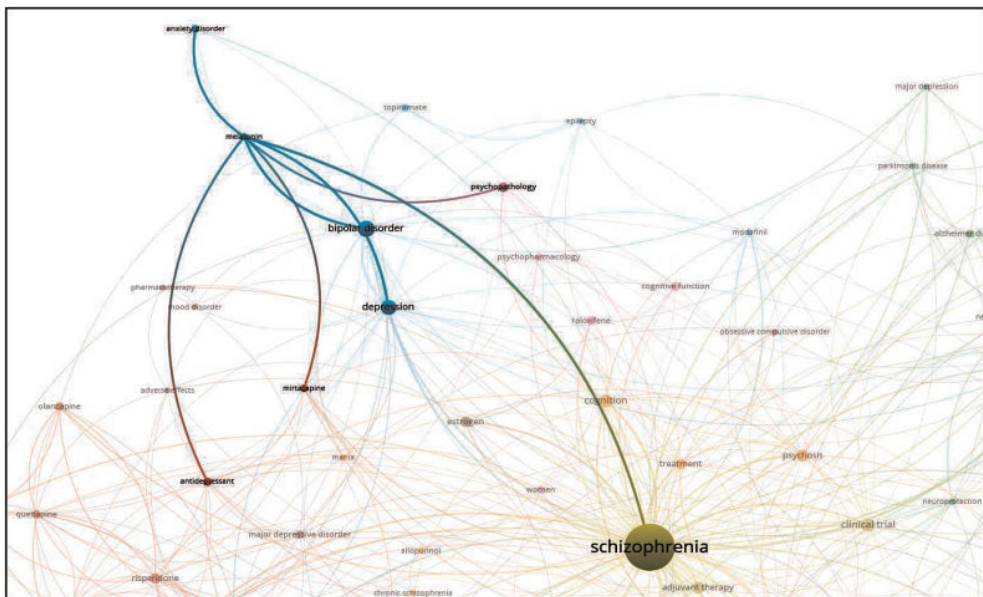


Figure 1. Melatonin cluster, all keywords connected to melatonin.

In this first analysis, all the keywords related to melatonin were referred to as melatonin clusters. As shown in Figure 1, the keyword melatonin is not much connected with other keywords. This suggests that melatonin has not been extensively studied in the last twenty years. Keywords connected to melatonin were schizophrenia, anxiety disorder, psychopathology, bipolar disorder, depression, mirtazapine, and antidepressant. This finding can

be understood because previously interrelated studies have been carried out, but not much. A recent study suggests that melatonin plays a role in the pathophysiology of schizophrenia. A decreased melatonin secretion at night was found in drug-free paranoid schizophrenic patients (Wynchank *et al.* 2016) Chronic treatment with antipsychotics can improve psychotic symptoms but does not normalize basic melatonin levels (Anderson & Maes 2012). Impaired melatonin secretion can also occur in the acute phase of depressive disease (Tonon *et al.* 2021) The treatment of mirtazapine antidepressants can provide several benefits for negative symptoms and increase the secretion of melatonin at night in schizophrenic patients since melatonin can control dopamine signaling (Sudha TY *et al.* 2021) Abnormalities in melatonin levels also occur in people with bipolar disorder due to light-triggered melatonin suppression, delayed melatonin secretion, and decreased melatonin levels at night. People with anxiety disorder also experience changes in melatonin levels. Thus, administering melatonin can improve the quality and duration of sleep, as well as relieve anxious symptoms (Moon *et al.* 2022).

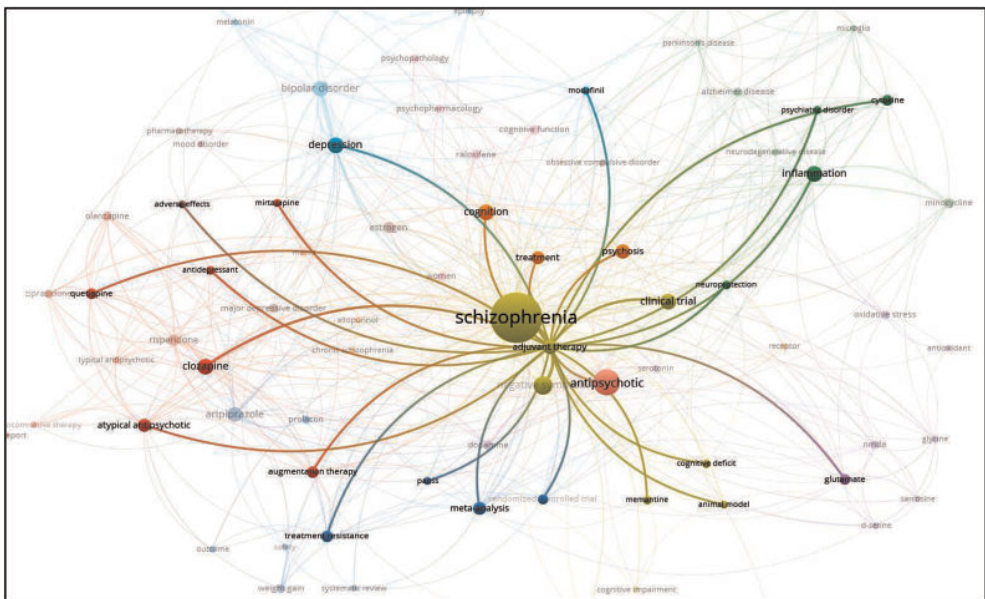


Figure 2. Adjuvant therapy cluster, all keywords connected to adjuvant therapy.

In the second analysis, all the keywords associated with adjuvant therapy were referred to as adjuvant therapy clusters. As shown in Figure 2, the keyword adjuvant therapy is much connected with other keywords. This suggests that adjuvant therapy has been extensively studied in the last twenty years. Keywords connected to adjuvant therapy were schizophrenia, modafinil, cytokine, psychiatric disorder, inflammation, depression, cognition, treatment, psychosis, clinical trial, neuroprotection, adverse effects, mirtazapine, antidepressant, quetiapine, antipsychotic, negative symptom, clozapine, atypical antipsychotic, augmentation therapy, panss, meta-analysis, randomized controlled trial, memantine, cognitive deficit, animal model, glutamate, and treatment resistance. Studies regarding adjuvant therapies which are beneficial in schizophrenia management are constantly evolving. Common adjuvants include lithium, curcuma, modafinil, memantine, and antidepressants such as mirtazapine. However, the administration of adjuvant therapy is still controversial because of its small or sometimes absolutely non-existent benefits (Andrade *et al.* 2015;

Johnson & Kotermanski 2006; Ryskalin *et al.* 2021; Saavedra-Velez *et al.* 2009; Small *et al.* 2003; Wu *et al.* 2015) Although schizophrenic patients do not always experience depression, many of the negative and cognitive symptoms of schizophrenia are very similar to those of depression. Therefore, adjuvant antidepressant mirtazapine can be beneficial for schizophrenic patients by improving the negative symptoms and increasing melatonin secretion at night (Perry *et al.* 2018; Sudha TY *et al.* 2021) Further psychopathological improvements directly implicate the presence of inflammatory pathways in the pathophysiology of schizophrenia (Miller & Buckley 2016).

The third analysis focused on studying melatonin as an adjuvant therapy. We found that studies on the administration of melatonin as an adjuvant therapy for people living with schizophrenia reached a peak in 2009 but then decreased and started to increase again in 2021 (Figure 3). This analysis was done by adding the keyword melatonin to Query 1, so we have Query 2 as follows:

```
( ( TITLE-ABS-KEY ( "adjuvant therapy" AND schizophrenia ) ) ) AND ( melatonin ) AND ( LIMIT-TO ( PUBYEAR, 2022 ) OR LIMIT-TO ( PUBYEAR, 2021 ) OR LIMIT-TO ( PUBYEAR, 2020 ) OR LIMIT-TO ( PUBYEAR, 2019 ) OR LIMIT-TO ( PUBYEAR, 2018 ) OR LIMIT-TO ( PUBYEAR, 2017 ) OR LIMIT-TO ( PUBYEAR, 2016 ) OR LIMIT-TO ( PUBYEAR, 2015 ) OR LIMIT-TO ( PUBYEAR, 2014 ) OR LIMIT-TO ( PUBYEAR, 2013 ) OR LIMIT-TO ( PUBYEAR, 2012 ) OR LIMIT-TO ( PUBYEAR, 2011 ) OR LIMIT-TO ( PUBYEAR, 2010 ) OR LIMIT-TO ( PUBYEAR, 2009 ) OR LIMIT-TO ( PUBYEAR, 2008 ) OR LIMIT-TO ( PUBYEAR, 2007 ) OR LIMIT-TO ( PUBYEAR, 2006 ) OR LIMIT-TO ( PUBYEAR, 2005 ) OR LIMIT-TO ( PUBYEAR, 2004 ) OR LIMIT-TO ( PUBYEAR, 2003 ) ) AND ( LIMIT-TO ( LANGUAGE, "English" ) )
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From the query, 18 documents were derived with the distribution of publication year as follows:

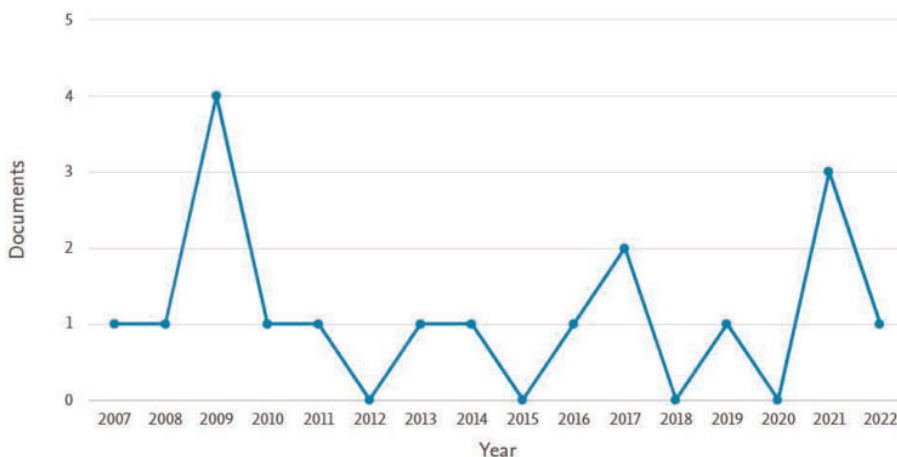


Figure 3. Distribution of publications with keywords related to schizophrenia, adjuvant therapy, and melatonin.

Out of the 18 articles and reviews, there are only six articles that are directly related to melatonin in their research topics, namely the research of Maldonado *et al.* (2009), Rozas (2009), Verster (2009), Anderson *et al.* (2013), Martone (2017), and Geoffroy *et al.* (2019) studies.

Furthermore, in addition to schizophrenia, three other keywords were found in the melatonin and adjuvant therapy clusters simultaneously, namely depression, antidepressant, and mirtazapine. If these three keywords are added as filters in Query 2, only 1 article will be obtained, namely Rozas (2009). A new trend has been observed in the development of double-action drugs that can be used in the therapy of depression, bipolar, and schizophrenia; melatonin seems to be the right candidate (Rozas 2009). Melatonin has the prospect of being an adjuvant therapy for psychiatric symptoms due to its anti-inflammatory, anti-nociceptive, anxiolytic, and detoxifying drug effects and has minimal side effects (Maldonado *et al.* 2009).

4 CONCLUSION

Visually melatonin has been related little to previous studies over the past 20 years. This finding suggests that melatonin is still relatively rarely studied despite having a positive impact on schizophrenic patients. Studies on melatonin as adjuvant therapy in schizophrenic patients will fill the gap in the lack of such research. This prospect deserves to be discussed further, considering that, in general, melatonin naturally regulates the sleep-wake cycle. It scavenges free radicals, boosts antioxidant enzymes, and maintains cellular membrane integrity.

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Spirituality and medical education: Bibliometric analysis of the current state of the art and perspective

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ABSTRACT: To be able to understand the latest research on spirituality and medical education, this research evaluates relevant themes related to spirituality and medical education through bibliometric analysis with the keyword “spirituality and medical education” as input. In this study using the Scopus database because it is considered ideal in bibliometric analysis. VOSviewer software is adopted as a bibliometric analysis tool for visualizing networks, authors, journals, and author keywords. The analysis conducted on August 15, 2022 found a total of 763 documents in the period 1986–2022. The results showed that in the past 36 years, the number of publications of articles on spirituality and medical education has grown significantly. The United States is the country with the most article publications in the world with lead authors, and research institutes involved. The Journal Religion of Health became a leading journal with regular publications. Spirituality and medical education are the subjects of the presented bibliometric analysis, which provides pertinent information on these topics. Spirituality plays an important role in medical education, as it can boost resilience and well-being and prevent burnout.

1 INTRODUCTION

Everyone has a kind of spiritual experience (Nahardani *et al.* 2019). Spirituality is the formation of values and directions of individual life in the world. It is an inner connection with oneself, others, the universe, nature, and transcendent affairs. Spirituality is a complex concept that includes dimensions such as meaning and purpose of life, love, respect, peace, compassion, hope, and peace. Spirituality can improve their quality of life and health behaviors. This may be the reason why dealing with spiritual care is currently emphasized in almost all disciplines, namely, medicine, nursing, social work, clergy, psychology and education (Papaleontiou-Louca *et al.* 2023). According to WHO, human beings have a variety of biological, mental, social, and spiritual characteristics. This definition emphasizes the role of spirituality in holistic health (Nahardani *et al.* 2019).

Education is a process of communication that contains a transformation of knowledge, values and skills that lasts a lifetime outside and inside the school. The learning process is influenced by intrinsic factors and extrinsic factors. Intrinsic factors come from within and have a greater role in influencing the spirit of learning such as the need for autonomy, competence and so on (Sari *et al.* 2016). Knowledge of medical education and teaching skills are self-reported as important learning outcomes for medical students (Onorato *et al.* 2022). Continuum framework for the 3 phases of formal medical education i.e. basic medical education,

postgraduate medical education, and continuous professional development (Lim 2020). Medical education is important in educating a medical student to be printed as a good doctor.

The health care system is only one aspect of the abstract and complex concept of spirituality in medical education. Overall, addressing its importance and promoting spirituality as a significant indicator of health is a key component of medical education (Wenham *et al.* 2021). Spirituality is a mental and multidimensional concept associated with the health care system. Therefore, it is very important to train health workers given their importance and relevance to the delivery of health services (Nahardani *et al.* 2019).

This research is a bibliometric analysis of various articles on spirituality and medical education. Bibliometric techniques include content analysis, keyword co-event analysis, co-citation analysis, and co-authoring analysis in addition to text analysis and citation analysis. (Dias 2019). VOSviewer is a vital analytical tool used in biblio-metric analysis (Van Eck & Waltman 2017). Broad word info metrics or in more specific phrases, scientometric, are very similar to bibliometric analysis. Another well-known example is webometrics that checks various web parts (Ellegaard & Wallin 2015).

Bibliometric analysis identifies a collection of literature. Initially, bibliometric analysis was known as citation analysis. However, the proliferation of bibliometrics is increasingly being used to provide data on the relationships between different authors, groups, fields of study, institutions, etc. It can be used to evaluate contributions in the field of study by authors, institutions, and even countries. Today, it has progressively developed into a research center in several sectors (Ahmad & Slots 2021; Bashir *et al.* 2021; Celik *et al.* 2021). Despite the advantages, careful consideration should be taken when analyzing bibliometric data. The majority of bibliometric criticism centers on the claim that impact, as measured by citation indicators, does not necessarily signify quality. In addition, publishing and citation trends in different fields will probably be very different. Therefore, strict use is required for direct evaluation of publications and citation metrics for various fields (Napitupulu 2021).

2 METHODS

2.1 *Data source and search methods*

Data collection was carried out on August 15, 2022 using Scopus as an article service provider. Scopus is the largest scientific database with the best quality and reputation that exists today. Scopus also provides a variety of peer-reviewed journal articles (Baas *et al.* 2020). Data search is carried out using keywords related to spirituality and medical education. The keywords used are “Spirituality and Medical Education”. The topics we have determined are entered into the search engine in the journal Scopus and there are various articles with the topic of spirituality and medical education as many as 763 articles. This research does not require ethical clearance because it does not use living things as objects of research.

2.2 *Data analysis*

The documents in the study were collected from the Scopus data platform, which is considered an ideal database for bibliometric analysis that includes information published in indexed journals in several areas of knowledge. This database has been widely used in bibliometric analysis. The search is carried out in the database and the evaluation of the obtained documents is divided into three phases: (PHASE 1) definition of search criteria for identifying records in the Scopus database and refinement of retrieved records (collection phase data); (PHASE 2) documents are exported to VOSviewer software for bibliometric analysis of publications, authors, countries, institutions, journals, and areas (data visualization phase); and (PHASE 3) data analysis to identify key themes addressed in developed research on spirituality and medical education.

3 RESULTS AND DISCUSSION

In this section will be described about statistical data based on the Scopus journal on spirituality and medical education. As already mentioned above that the articles that have been searched in the Scopus database show the number 763 articles. Articles are analyzed by publication, author, country, institution, journal, and area (data visualization phase).

3.1 *Publication rate of articles on spirituality and medical education*

Figure 1 shows research trends on spirituality and medical education based on articles published per year. In general, the increase in the publication of articles on spirituality and medical education began around 1986 and increased greatly by marking exponential charts. The trend of article publishing has moved dynamically to date and has been developing for approximately 36 years.

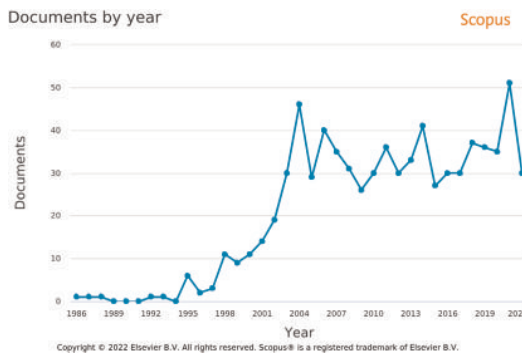


Figure 1. Tendency to publish spirituality and medical education articles per year.

3.2 *Author with the most articles on spirituality and medical education*

Figure 2 shows the 10 authors with the most publications on spirituality and medical education. Koenig H.G. is the author with the most publications in the list of 23 articles. Lucchetti Giancarlo has written as many as 20 articles. Followed by Puchalski, Lucchetti Alessandra, Anandarajah. Balboni Tracy and Peteet wrote articles with the same number of publications, namely 8 articles. Balboni Michael, DiLalla, Curlin are also part of the authors of articles on the topics of spirituality and medical education. The interesting thing about this author is that 8 of the 10 authors of the most spirituality and medical education articles are from the United States.

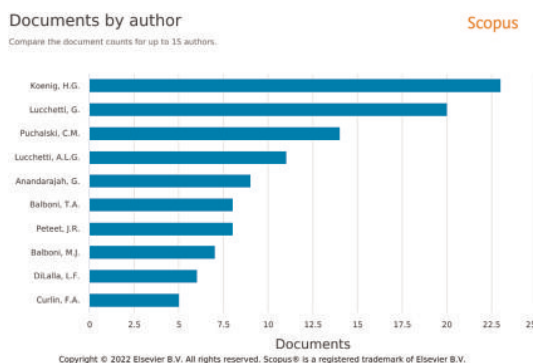


Figure 2. The 10 authors with the most publications on spirituality and medical education.

3.3 Journals with the most publications on spirituality and medical education

Figure 3 shows the 10 journals with the most publications on spirituality and medical education. The 10 journals accounted for 168 articles out of 763 total number of article publications. The leaders of journals based on the table are the Journal of Religion and Health with 39 articles and Academic Medicine with 25 articles. Followed by Academic Psychiatry with a total of 17 articles. In general, it is seen that the majority of differences between individual journal publications are not so significant. Then, in other journals in order as shown in Figure 3.

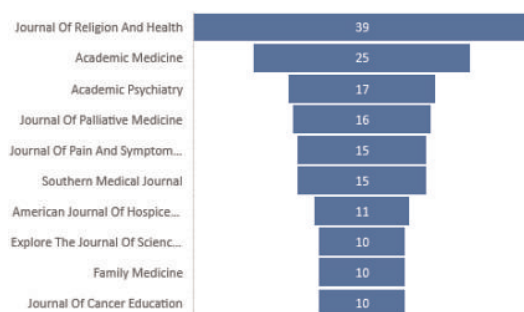


Figure 3. The 10 journals with the most publications on spirituality and medical education.

3.4 Topic

Area Visualization Using VOSviewer analysis will be presented to visualize results based on frequently appearing keywords. This study shows bibliometric analysis into data network visualization as in Figure 4 and overlay visualization as in Figure 5.

In Figure 4, the visualization of each keyword related to spirituality research is symbolized by the shape of a circle in VOSviewer. Keywords are more important because the more they appear, the bigger the circle. The frequency of occurrence affects the size of the circle in each keyword. Naturally, the word spirituality became the top research topic because the frequency of occurrence was the highest. Each circle has a different color because it follows its cluster. (Van Eck & Waltman 2017).

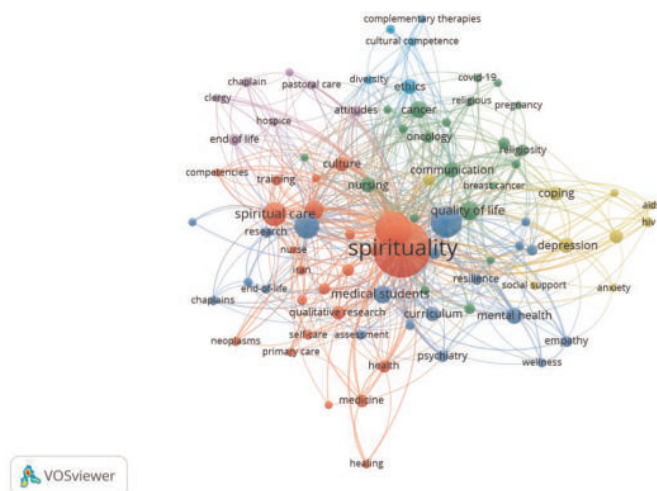


Figure 4. Network visualization spirituality and medical education based on scopus using VOSviewer.

Figure 5 shows the research topics by year. However, most of the keywords appeared in 2010 to 2018. The more yellow the color indicates the newer the article with the keywords discussed, and vice versa with the more purple color.

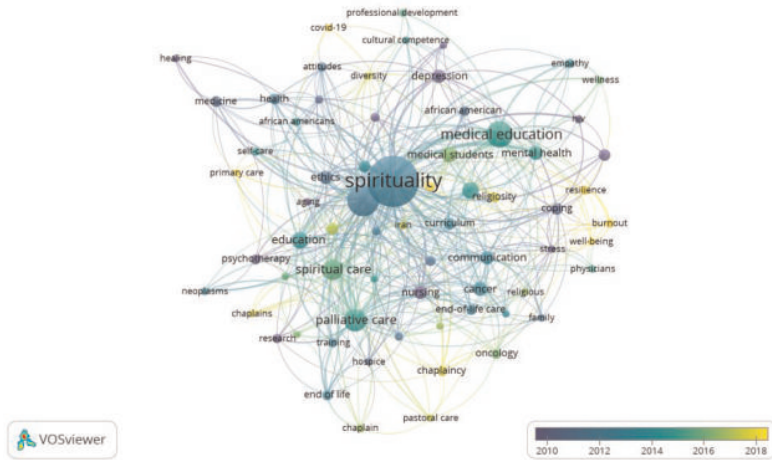


Figure 5. Overlay visualization spirituality and medical education based on scopus using VOSviewer.

4 DISCUSSION

All peer-reviewed journals in the field of spirituality research and medical education were studied using bibliometric analysis from the Scopus database. The literature on spirituality and medical education grew dynamically every year for 36 years. The findings of this study reveal trends in the study of spirituality and medical education, as well as trends in publications (peer-reviewed journals), contributing authors, and publisher journals.

Furthermore, using keyword collection in clusters, cluster analysis identifies key areas of study in the field of spirituality. As a contribution of this work, keyword analysis of words with fewer occurrences provides a possible subject of research (Napitupulu 2021). It is very useful because it can provide us with information on the topic under study for 36 years. VOSviewer also points to the relationship between one topic and another, especially research in the field of spirituality. For example, “wellness” is indicated by a small circle. This shows that there is still little research linking spirituality with wellness, so it can be an opportunity for authors to raise this theme. Similarly, “medical education” is shown by a sizable circle which means quite a lot of articles linking spirituality with medical education.

The concept of spirituality is intrinsically an educational topic because education offers the best opportunity for human spirituality to be realized. First and first, doctors need to understand what spirituality is, what it means for people, and how it gives them the meaning of incidents. Then, in order to give it effectively to their students, they must use it as an important foundation for professional ethics. By offering patients exciting opportunities, doctors can help patients achieve favorable outcomes by observing and examining the expression of spirituality in patients using the characteristics and antecedents that emerge from the analysis of current concepts. In addition, a general understanding of how spirituality is used in the field of care and education will result from relative agreement on how to define it in medical education (Napitupulu 2021).

As professionals, doctors use spirituality in a way that goes beyond their training and expertise in diagnosing and treating diseases, managing suffering, and preventing disease. On

the contrary, each of these activities requires that doctors have qualities consistent with their profession, which when combined creates professionalism. As a result, medical professionals need to be educated about the virtues of spirituality. One of the precursors, underlying causes, and the result of spirituality is education. Therefore, it seems that initiatives to continue education and teach spirituality to medical students will help doctors become more empowered to use spirituality (Nahardani *et al.* 2019).

5 CONCLUSION

This study used bibliometric analysis to review all peer-reviewed journals from the Scopus in the field of spirituality research and medical education. The study also aims to update and improve bibliometric analysis. Due to the limited use of VOSviewer in the bibliometric study of spirituality and medical education literature, mapping and visualization of bibliometric data using the VOSviewer program has been demonstrated effectively. The idea that spirituality should be given more weight in medical education is an intriguing one. Doing so can help improve resiliency and wellbeing, as well as protect against burnout.

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Correlation between Neutrophil-to-Lymphocyte Ratio and length of stay in pregnant women with COVID-19

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ABSTRACT: There is evidence that climate change is affecting COVID-19. We found that absolute humidity and temperature are associated with influenza epidemics and contribute to epidemic progression. In the tropics, SARS-CoV-2 appears to have higher survival and infection rates than influenza viruses. Interruption of aerosol transmission of influenza virus has been described with temperature fluctuations greater than 30°C. However, there is no definitive cure for COVID-19. Factors that influence COVID-19, such as the neutrophil-to-lymphocyte ratio (NLR), need to be identified. The aim of this study was to identify the correlation between the Neutrophil-to-Lymphocyte Ratio and length of hospital stay in pregnant women with COVID-19. This study is an analytical observational study with a cross-sectional design. Statistical test by unpaired T-test with $p < 0.05$. A total of 34 subjects were taken, 16 in K1 and 18 in K2. Subjects had a mean age of 31.59 ± 8.67 years and the majority were in the third trimester. Unpaired T-test results showed no significant association between her NLR score and length of hospital stay ($p = 0.749$) in COVID-19 pregnant patients.

1 INTRODUCTION

1.1 COVID-19

By January 2021, the number of new cases of COVID-19 from various countries around the world is projected to continue to rise at staggering numbers. The Southeast Asia region alone is estimated to have up to 200,000 new cases each week. Indonesia is on the list of the top five countries with the newest cases in Southeast Asia (WHO 2020). COVID-19 is still a problem in Indonesia, especially in Central Java (Prabowo 2021a). The number of pregnant women cases of COVID-19 is also increasing. Pregnant women are at increased risk of COVID-19 during and after pregnancy and in their babies. Pregnant women are at increased risk of more serious illness, morbidity and mortality compared to the general population. This is due to an altered immune response (Nurinasari 2021). There are theories about the link between climate change and pandemics such as the SARS-Cov-2 (Severe Acute Respiratory Syndrome Coronavirus-2) outbreak. Climate change and COVID-19 are global public health challenges. Both aggravate and aggravate each other. The COVID-9 pandemic has shown our ecosystem's inability to defend itself. Environmental destruction and climate change may increase the risk of viruses being transmitted from animals to humans and vice versa (Prabowo 2021b). We found that absolute humidity and temperature are associated with influenza epidemics and contribute to epidemic progression. In the tropics, SARS-CoV-2 appears to have higher survival and infection rates than influenza virus. Blocking aerosol

transmission of influenza virus is described with temperature fluctuations greater than 30°C (Abdelrahman 2020).

1.2 *Immune response to COVID-19*

The immune system's response to COVID-19 infection activates immune cells, interleukin-1 β (IL-1 β), interleukin-6 (IL-6), interferon- γ (IFN γ), monocyte chemoattractant protein to produce pro-inflammatory cytokines such as -1 (MCP1), interferon-gamma-induced protein-10 (IP-10), and tumor necrosis factor-alpha (TNF-alpha). In some cases, proinflammatory cytokines are overproduced and unregulated, which can lead to cytokine storms (Phoswa & Khaliq 2020). This cytokine storm underlies a variety of morbidities, including acute respiratory distress syndrome (ARDS), multiple organ failure, and severe death in his COVID-19 case. Therefore, the patient's inflammatory status is an important factor in the management of COVID-19 cases (Nile *et al.* 2020). Inflammatory status, according to several of studies, can be estimated using the patient's NLR (Neutrophil to Lymphocyte Ratio), Platelet to Lymphocyte Ratio (PLR), & Mean Platelet Volume (MPV) profiles (Qin *et al.* 2016). NLR as a marker of inflammatory status has been shown to work as a predictor of the severity of the infection & the risk of mortality in COVID-19 patients during hospitalization (Liu *et al.* 2020). NLR has also been shown to be a predictor of patient length of stay. According to previous studies, patients with higher NLR values are at risk for longer hospital stays (Yang *et al.* 2020).

1.3 *Pregnant women and COVID-19*

Pregnant patients with COVID-19 have their own clinical characteristics & laboratory test results & are different from COVID-19 patients in general. Pregnant patients with COVID-19 who were admitted to Wuhan Hospital in China were reported to have higher neutrophil values & lower mean lymphocytes compared to non-pregnant patients (Wang 2020). Pregnant women patients have a varied average length of hospitalization & tend to experience worsening if infected with COVID-19. According to a case report of 66 female COVID-19 patients in China, the average length of stay for COVID-19 pregnant women was 17.3 days with the proportion of pregnant patients diagnosed with severe COVID-19 being higher than non-pregnant patients (Yin *et al.* 2020). This is in line with reports from the United States which showed that pregnant women, compared to non-pregnant women, had a higher hospitalization rate (Qeadan *et al.* 2021). Therefore, pregnant women receive special attention & have their own recommendations for hilling COVID-19 (Aziz *et al.* 2021).

1.4 *Inflammatory status marker*

NLR is a simple marker of inflammatory status markers. It is not clear whether the higher the inflammatory status, the longer the hospitalization for pregnant women with COVID-19. Therefore, the purpose of this study was to determine the correlation between Neutrophil-Lymphocyte Ratio & Length of Hospitalization in Pregnant Women with COVID-19.

2 MATERIALS AND METHODS

2.1 *Study design*

This research is a cross-sectional study, with an analytic observational study design. The health research ethics committee from the Faculty of Medicine, Sebelas Maret University, approved the ethical approval.

2.2 Population and study setting

The study population was pregnant women who had been diagnosed with COVID-19 between April 2020 and August 2021 and had to be admitted to UNS hospital. Inclusion criteria were pregnant patients, who were confirmed positive for COVID-19 by TCM/RT-PCR swab test requiring hospitalization & NLR check performed. Exclusion criteria were patients with incomplete medical records, such as age and diagnosis of COVID-19, patients with congenital, immunocompromised, and chronic diseases that prolong hospital stay, and patients who died. We collected 34 samples with a mean gestational age of 37 to 40 week.

2.3 Variables

In this study, the researcher meant the NLR value obtained from complete blood checks in pregnant women infected with SARS-CoV-2. NLR is neutrophils divided by lymphocytes. The length of hospitalization is in units of days from day 1, which is the day the subject is registered as a patient at UNS (Universitas Sebelas Maret) Hospital until the 7th day, which is the day the subject is subjected to a follow-up swab examination according to the guidelines. Statistical analysis with unpaired T-test, the significance of $p < 0.05$.

3 RESULTS AND DISCUSSION

From 34 samples, it was found that the mean age of patients in both groups was entirely in the third decade (33.31; 30.06 years). The majority of study subjects had a gestational age of 37–40 weeks (75; 83.3%). There were only 3 & 2 patients who had gestational age < 37 weeks in each group (18.8; 11.1%). Meanwhile, there was only 1 patient with gestational age > 40 weeks in each group (6.3; 5.6%).

Data on the mean and standard deviation of NLR values based on length of stay are presented in the table below:

Table 1. Comparison of NLR on length of hospitalization.

The length of hospitalization	Mean NLR	P value
< 7 days	5.86 ± 2.85	0.749
≥ 7 days	7.15 ± 4.49	
Total	6.50 ± 3.76	

Based on Table 1, there was a slight difference between the characteristics of patients who were hospitalized for < 7 days & those who were hospitalized for ≥ 7 days.

The same result is shown more clearly through the diagram below:

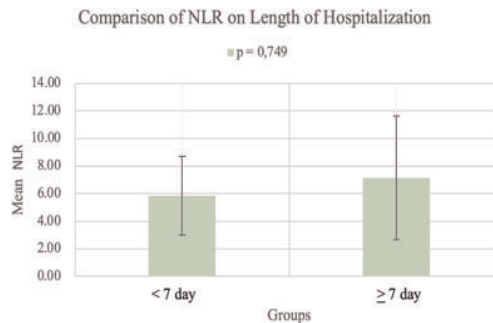


Figure 1. Comparison of NLR on length of hospitalization.

A patient's length of stay is influenced by several factors, including COVID-19 treatment guidelines used, severity of illness, level of staff expertise, bed, equipment required, and patient characteristics such as age and comorbidities (Rees 2020). Recent studies have shown that NLR as a patient's inflammatory status can function as a predictor of length of stay. According to the research of Yang A et al, there is a difference in the length of stay of COVID-19 patients between patients with a different NLR values. Patients with an NLR greater than 3.3 should receive more attention because 46.1% of the 93 moderate-grade patients progressed to severe cases within an average of 6.3 days. Meanwhile, patients with ages of less than 49.5 years & NLR of less than 3.3 will usually finish hospitalization with a total length of stay of 13.5 days (Yang 2020).

The study results in Table 1 and Figure 1 are consistent with those of Yang A *et al.* It is true that the mean NLR and standard deviation values were lower for the patients with less than 7 days of hospitalization than those with more than 7 days of hospitalization. However, in this study, patient in the hospitalized group found no significant difference in the NLR values, only a slight difference. The results of this study indicate that NLR values has not been able to predict length of stay for COVID-19 patients.

It is noted that this study is limited by the small sample size which allows bias. In addition, this study was conducted using secondary data obtained from medical record data of patients at UNS Hospital, so this study has the disadvantage of not including variables that are confounding factors & taking blood samples with non-uniform time. Another possible reason the results are not significant is that three changes have been made to guidelines for treating COVID-19 in mothers (pregnancy, delivery, & postpartum) in Indonesia, namely edition 1 on March 15, 2020, revised edition on August 8, 2020, & revised edition on June 22, 2021.

4 CONCLUSIONS

There is no relationship between NLR & length of stay in pregnant women with COVID-19. To leverage climate & disaster resilience, especially during the pandemic, decision-making needs to be more informed about the predictors of length of hospital stay. Suggestions for further research are that further research should be carried out with a larger sample size to minimize bias & it is recommended that the therapeutic guidelines be equated so as not to affect the results of the main analysis.

ACKNOWLEDGEMENT

We would like to acknowledge The Directorate General of Higher Education (Ditjen Dikti) Indonesia Ministry of Education, Culture, Research, & Technology (Kemendikbud Ristek) for providing funding for this research.

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The effectiveness of electroacupuncture for treating labor pain in primary healthcare: A preliminary study

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ABSTRACT: Labor pain is caused by nociceptor activation following ischemia by distension lower part of the uterine and cervix. The majority of women experience pain during childbirth. However, not all women feel the same way. Additional therapy can be used to alleviate labor pain. Electroacupuncture (EA) is a modern variation of acupuncture that uses electrical energy. It has been proven to reduce nociceptors activation-causing pain. This study aims to evaluate the effectiveness of EA on labor pain. This experimental study was conducted for two months in Indonesian primary healthcare. A total of 11 women received EA thrice at the minute of 15, 30, and 60 during their active first stage until the second stage of delivery. The needle insertion points were LI4, ST36, SP6, and several uterine innervation-associated segmental points. EA used 2/100 Hz alternating frequency and 0.1–0.3 mA intensity with 20 minutes adjustment. Numbering Analog Scale (NAS) was used to evaluate the amount of labor pain. The results showed a significant decrease in NAS between pre-intervention and 15-minute post-intervention (7.909 ± 0.700 vs. 6.909 ± 0.539 , $p = 0.005$). NAS pre-intervention also significantly reduced after 30 and 60-minute intervention ($p = 0.001$). However, there was no further significant decrease in NAS from 30-minute to 60-minute post-intervention (4.909 ± 0.831 vs. 4.454 ± 0.522 , $p = 0.383$). There were no prolonged second stage of delivery, post-partum hemorrhage (PPH), and neonate asphyxia to be reported. EA is effective and significant for reducing labor pain, strengthening uterine contractions, and accelerating the second stage of delivery, as no side effects were reported. It also can be applied in primary healthcare as EA is a simple medical device and widely available.

1 INTRODUCTION

Labor is a physiologic process during which the fetus, membranes, umbilical cord, and placenta are expelled from the uterus. The term ‘normal labor’ is defined in academic literature, and health policy has more generally referred to birth without or with limited clinical intervention (Smith *et al.* 2020). Even though childbirth is a natural process, often a high extent of emotional stress, anxiety, fear, and pain experienced during labor causes high levels of catecholamine and leads to reduced uterine activity, prolonged labor, and neonatal asphyxia (Stjernholm *et al.* 2021). Thus, labor pain management could improve both maternal and neonatal outcomes.

Stretching and distention of the lower uterine segment and dilatation of the cervix stimulate mechanoreceptors to transmit painful impulses during the first stage of labor. These impulses traverse visceral sympathetic nerves at the T10-L1 spinal cord. During the active phase of the first stage and second stages of labor, perineal stretch stimulates somatic pain nerves through the pudendal nerves from S2-S4 (Hensley *et al.* 2017). Those pains can be felt in the area of the waist, and abdominal area and radiates towards the thighs. Despite the difference in pain perception among women with the same pain level, the intensity of pain can be determined by asking the level of intensity according to a pain scale such as the Numbering Analog Scale (NAS) (Pietrzak *et al.* 2022).

Pharmacological pain management remains controversial as it can penetrate the placental barrier and harm both mother and fetus. Acupuncture is a complementary treatment that has been widely used to alleviate pain and neurological deficits. Fine needle insertion stimulates the central nervous system and releases chemicals into the muscles, spinal cord, and brain. These releases promote hemostasis and natural healing of body recovery (Ernst *et al.* 2011). Various types of stimulation by acupuncture have been developed, such as electroacupuncture (EA), which utilizes electrical stimulation with needle manipulations. The use of acupuncture as supplementary pain management during labor has been studied (Brown & Schaffir 2019; Neri *et al.* 2018; Williams *et al.* 2020). They showed favorable outcomes for both maternal and neonatal. However, there is still limited study regarding EA for labor pain.

Nowadays, EA for pain labor treatment in Indonesia is very rare in primary-to-tertiary healthcare as EA is neither a routine nor mandatory treatment protocol during childbirth (Tsuei *et al.* 1977; Qu & Zhou 2007). However, achieving optimum maternal and neonatal outcomes by labor pain treatment by EA can be reached as EA is widely available and easy to use. This preliminary study aims to determine the effectiveness of EA in treating labor pain in primary healthcare. Furthermore, we also investigate if it is associated with a prolonged second stage of delivery, PPH, and neonate asphyxia.

2 METHODS

This preliminary experimental study was performed from early July to late August 2023 at a single primary health care in Indonesia. A total of 11 37-week pregnant women with normal conditions such as fetal head presentation and no history of medication to reduce labor pain were included in this study. The exclusion criteria were uterine-placental abnormalities, head-pelvic disproportion, hydramnios, twin fetuses, congenital fetal abnormalities, hypertension, pre-eclampsia, and metabolic diseases. They received EA thrice at the minute of 15, 30, and 60 during their active phase of the first stage to the second stage of delivery. The active phase of the first stage was indicated by 4 cm of the cervical opening.

The acupuncture needle was 0.30×40 mm. The needles insertion point were LI4, ST36, SP6, and several uterine innervation-associated segmental points of BL20, BL21, BL31, and BL32 (Figure 1). The general points were LI4, ST36, and SP6. LI4 is located on the back of the hand, and ST36 and SP6 are on the lower leg. We also use the segmental points of uterine



Figure 1. Electroacupuncture treatment and acupuncture needle positions.

innervation, such as BL 20, BL 21, BL 31, and BL 32. Pishu (BL 20) is located on the back at the level of the lower border of the spine processes. TXI 1.5 cun is lateral to the median line. BL-21 Weishu is at the back lower border of the spine process. TXII 1.5 cun is lateral to the median line. BL-31 Shangliao is located above the sacral foramen I and 1 cun lateral to the midline below the transverse processes of the fifth lumbar. BL-32 Tzuliao is above the second sacral foramen in the anteroinferior part of the posterior superior iliac spine. BL-33 Chungliao is located above the third sacral foramen in the anteroinferior part of BL-32.

EA used 2/100 Hz alternating high-frequency and 0.1–0.3 mA intensity with 20 minutes adjustment. Dense-disperse wave from transcutaneous electro-stimulator was adjusted according to an amplitude intensity tolerable to patients. Numbering Analog Scale (NAS) was used to evaluate the amount of labor pain at the minute of 15, 30, and 60 as well. NAS ranging from 0 to 10. Its pain interpretation is mild (0–4), moderate (5–7), and severe (8–10). Furthermore, the neonate asphyxia was assessed thrice by APGAR score at 1, 5, and 20 minutes after birth. The duration of the second stage of delivery was evaluated by partograph. The presence of PPH was indicated by at least 1,000 mL of total blood loss.

The effectiveness of EA was evaluated by numerical statistics. Mean comparison of One-Way ANOVA and Post-Hoc Tukey of pre-intervention vs. 15, 30, and 60-minute post-intervention of EA were used to determine the NAS significance differences. A p-value of 0.05 or lower is considered statistically significant. IBM SPSS Statistics 22.0 for Windows was used to perform statistical analyses.

3 RESULTS

The study's demographic characteristics and the overall main result are presented in Table 1. The mean comparison of NAS between pre-intervention vs. 15, 30, and 60-minute post-intervention of EA is presented in Table 2. There was a significant NAS decrease between pre-intervention and 15-minute post-intervention ($p = 0.005$). NAS pre-intervention also showed a significant reduction after 30 and 60-minute intervention ($p = 0.001$ for both). Meanwhile, there was no significant NAS decrease from 30 to 60 minutes post-intervention ($p = 0.383$).

Table 1. The demographic profile and main result of the study.

No.	Age (years)	Gravidity	NAS pre-intervention	NAS post-intervention			PPH	Second stage of delivery (minute)	APGAR score
				15'	30'	60'			
1	24	2	7	6	5	5	No	5	7/8/10
2	27	3	8	7	4	4	No	6	7/8/10
3	30	3	7	7	5	5	No	8	8/9/10
4	35	2	8	8	7	5	No	5	8/9/10
5	29	3	8	7	4	4	No	5	7/9/10
6	27	2	8	7	5	4	No	5	8/9/10
7	25	2	7	7	4	5	No	10	8/9/10
8	25	2	8	7	5	4	No	5	8/9/10
9	32	3	9	7	5	4	No	5	8/9/10
10	33	3	9	7	5	4	No	5	7/8/10
11	33	2	8	6	5	5	No	5	8/9/10

NAS, numbering analog scale; PPH, post-partum hemorrhage.

Table 2. The comparison of NAS between pre-intervention vs. 15, 30, and 60-minute post-intervention of EA treatment for labor pain (N = 11).

	Mean \pm SD	p-value**			
		Pre-intervention	15' post-intervention	30' post-intervention	60' post-intervention
Pre-intervention	7.909 \pm 0.700	–	0.005	0.001	0.001
15' post-intervention	6.909 \pm 0.539	0.005	–	0.001	0.001
30' post-intervention	4.909 \pm 0.831	0.001	0.001	–	0.383
60' post-intervention	4.454 \pm 0.522	0.001	0.001	0.383	–
p-value*		0.001			

SD, standard deviation.

* One-Way ANOVA

** Post-hoc Tukey

4 DISCUSSION

In Indonesia, primary health clinics provide midwife-assisted births under supervision from a physician. Nowadays, there is no EA treatment for labor pain in primary healthcare. This present study offers EA without any reported complications such as prolonged second stage of delivery, PPH, and neonate asphyxia. EA significantly ($p < 0.05$) reduced labor pain in all spontaneous childbirth women. The average NAS decrease was from 8 to 5 or 6. This pain-alleviating condition accelerated the second stage of delivery by strengthening uterine contraction. Furthermore, good uterine contraction will also prevent PPH. Additionally, the APGAR showed favorable outcomes in all newborns, suggesting EA has no adverse effect on both neonatal and maternal. Acupuncture stimulates antioxidant enzyme and surfactant development that leads to beneficial impacts on lung alveolar development and maturation during both pregnancy and delivery (Chen *et al.* 2005; Wong *et al.* 2013). A systematic review showed that acupuncture therapy during pregnancy and delivery results in few

adverse events when properly given. Its adverse event-related incidence was 193 per 10,000 acupuncture therapy in pregnancy. The study also showed no evidence of harm by LI4, SP6, or sacral points acupuncture (Park *et al.* 2014).

This present study used general acupuncture points such as SP6, LI4, and ST36. According to Traditional Chinese Medicine, SP6 is the meeting point of the 3 Yin channels of the legs (Spleen, Liver, and Kidney). These 3 Yin leg channels dominate menstruation, conception, pregnancy, leucorrhea, and the external genitalia. SP6 is also an important point for encouraging labor, assisting in cases of transverse presentation, and reducing pain during childbirth (Yesilcicek Calik & Komurcu 2014). LI4 is located on the highest spot of the muscle when the thumb and index fingers are brought close together. It produces strong actions to promote labor even promote the expulsion of a dead fetus. Furthermore, LI4 is considered to have an indication for labor induction (Chung *et al.* 2003). ST36 is located 1 *cun* lateral to the inferior border of the tibial tuberosity 1.5 *cun* below the skin's surface. It improves circulation in the pelvic organs (Liu *et al.* 2012).

The segmental acupuncture points used in this study were Shang Liao (BL31) and Ci Liao (BL32) and other related points. These dermatomes innervated by the nerves originated from LIV-V and SI-III of spinal cord segments that stimulate sympathetic and improved blood flow to the uterus (Smith *et al.* 2017).

Acupuncture influences the body hemostasis process, such as limbic-paralimbic-neocortical network system deactivation, which is responsible for pain perception, activation of serological endorphins receptors, and adrenocorticotrophic hormone release from the anterior pituitary. This process leads to a pain decrease during labor (Hui *et al.* 2010). Moreover, acupuncture stimulates oxytocin release from the posterior pituitary which will optimize uterine contraction to accelerate the labor process and prevent PPH (Pak *et al.* 2000).

This report had several limitations. The very nature of the preliminary study is that only a few patients (n = 11) participated. This makes cause-effect relationships difficult to establish compared to randomized-controlled trials. Furthermore, we recommend that future studies use pain-reliable measurements such as serum cortisol instead of subjective pain scale measurements.

5 CONCLUSION

This preliminary study showed that EA could significantly reduce labor pain according to NAS measurement in normal delivery women at primary healthcare. EA does not cause harmful effects on both maternal and fetal such as prolonged second stage of delivery, PPH, and neonate asphyxia, according to APGAR evaluation.

ETHICAL APPROVAL

Not applicable as all patients had signed informed consent for the acupuncture treatment. The written consents are available for review by the Editor-in-Chief of this journal on request.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

FUNDING

This article has been funded by an applied research excellence program of LPPM Universitas Sebelas Maret (Grant number: 260/UN.27.22/HK.07.00/2022).

AUTHOR CONTRIBUTION

All authors contributed equally to this manuscript. All authors read and approved the final manuscript.

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The potential of *Cinnamomum cassia* in lowering blood sugar levels in patients with type 2 diabetes mellitus

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ABSTRACT: Diabetes mellitus (DM) is a metabolic disease that is still a concern, leading cause of morbidity and mortality among the adult age group globally. Controlling diabetes is a constant challenge and treatment using drugs is expensive and has side effects in the future so natural remedies are being sought together. Cinnamon has become an attractive natural product because it is an herb, at a lower cost with few side effects and it has been hypothesized to have tremendous health benefits for lowering fasting blood glucose. The purpose of this study was to evaluate cassia cinnamon for diabetes mellitus. The author searched the PubMed, Scopus and ScienceDirect databases. with keywords including cinnamon cassia and diabetes mellitus; “cassia cinnamon AND serum blood glucose”; cassia cinnamon AND type 2 diabetes mellitus.

1 INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease that is still a concern, well-known as a leading cause of morbidity and mortality among the adult age group globally (Saeedi *et al.* 2019). Patients with diabetes mellitus continue to increase every year. this is evidenced by the number of people with diabetes mellitus in the world aged 20–79 years are living with diabetes 1 in 10 reaching 537 million. People the total population of the same age and is predicted to rise to 643 million by 2030. The prevalence of diabetes mellitus is estimated to increase until in 2045 it is predicted to reach 783 million (Federation 2022).

Management of diabetes mellitus with non-pharmacological approaches can be in the form of lifestyle changes, physical exercise, and medical nutrition interventions (Leite *et al.* 2020, Raveendran *et al.* 2018). In addition, pharmacological treatment is also carried out. Conventional use of hypoglycemic agents is a more expensive treatment which can cause several side effects which have also been associated with long term damage, dysfunction, and multiple organ failure, which is why many diabetics turn to traditional medicines with natural ingredients. Cinnamon has become an attractive natural product because it is an herb, at lower cost with few side effects and has been hypothesized to have extraordinary health benefits for lowering fasting blood glucose and assessing homeostatic models for insulin resistance rates (HOMA-IR), thereby bringing benefits for diabetic patients for the treatment of DM (Ranasinghe *et al.* 2012; Ulbricht *et al.* 2011; Zare *et al.* 2019). The genus *Cinnamomum* (Lauraceae) includes more than 250 species, among which *Cinnamomum cassia* (synonym: *C.*

aromaticum Nees, cassia cinnamon or Chinese cinnamon) are most commonly used as medicines (Nabavi *et al.* 2015). *C. cassia* contains almost 95 % cinnamaldehyde (Krieger *et al.* 2013). Cinnamaldehyde, an active component of cinnamon, has been investigated for insulin release and insulin receptor kinase regulation. Cinnamon may increase insulin sensitivity by inhibiting the enzyme protein tyrosine phosphatase 1B (PTPase 1B), which inactivates insulin receptors and by increasing the glucose-transporting molecules (GLUT4) required for glucose uptake by adipose and muscle cells from plasma (Anand *et al.* 2010; Medagama 2015). Cinnamon has plant parts that are effective and beneficial for health. This study aims to evaluate the effect of cassia cinnamon on blood sugar levels in diabetes mellitus.

2 GETTING STARTED

2.1 Search strategy and study selection

The search for articles was obtained by covering electronic databases, namely PubMed, Science Direct, and Scopus. Key words included cinnamon cassia and diabetes mellitus; “cassia cinnamon AND serum blood glucose”; cassia cinnamon AND type 2 diabetes mellitus. This review reports articles published in English from 2005 to 2022. After a search, all citations found were collated and uploaded to Mendeley Reference Management Software, and duplicates were identified. Guidelines for using Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Moher *et al.* 2009).

2.2 Assessment of study quality

The inclusion criteria were research articles using cassia cinnamon as a natural medicine. Studies that met the following criteria were selected and included: 1) Subjects included animals (rats) and humans with diabetes mellitus; 2) full text articles available at English; 3) all experimental, comparative, and clinical trials to date were searched. Diabetes mellitus was diagnosed using criteria based on clinical laboratory parameters for animals (Anand *et al.* 2010) and International Diabetes Federation Atlas 10th Edition (Federation 2022; Nam *et al.* 2021) for humans. outcome variables evaluated glycosylated hemoglobin (HbA1c), blood glucose and insulin.

3 RESULTS AND DISCUSSION

A flow chart of the article-finding process and the total number of articles discovered was shown in Figure 1. From three electronic databases and reference searches, we found 251 articles; then we excluded 86 duplicate articles, 165 review articles were filtered and 16 were

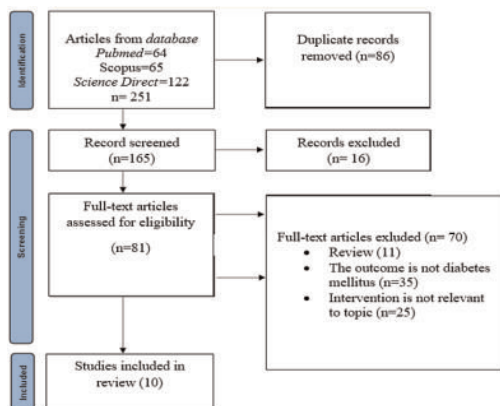


Figure 1. Flow chart of the study according to PRISMA.

excluded. 81 complete articles and assessed for eligibility. After that, 70 were excluded with non-diabetes mellitus results, intervention irrelevant.

Studying systematic reviews helped conclude cassia cinnamon related to natural medicinal uses. Results suggested *C. cassia* helped manage diabetes at 3–6 g per day. In addition, the chemical properties of *C. cassia* and *C. verum* differ considerably. Of note, *C. cassia* contains high levels of the potentially hepatotoxic constituent coumarin. A skin rash was the only adverse event reported (Shinjyo *et al.* 2020). To regulate the expression of genes in the field of molecular biology. Interleukin-6, interleukin-1, and tumor necrosis factor- are inflammatory cytokines. The cinnamon extract also increased the mRNA expression of insulin-sensitive genes, such as *Ir*, *Irs-1*, *Irs-2*, PI-3 kinase, and *Akt1*, and repressed genes associated with an increase in triacylglycerols, cholesterol, and apolipoprotein-B48 levels, etc. In laboratory experiments, cinnamon extract had also been shown to stimulate the expressions of phospho-p38 mitogen-activated protein kinase, c-Jun N-terminal kinase, and extracellular-signal-regulated kinase (Mandal *et al.* 2021).

A polyphenol that affects the expression of the insulin receptor, tristetraprolin, and GLUT4 is one of the potent anti-diabetic components of cinnamon extract (Cao *et al.* 2007). The oral administration of cinnamaldehyde (20 mg/kg bwt) significantly decreased plasma glucose concentration, glycosylated hemoglobin (HbA1C), serum total cholesterol, and triglyceride levels while also significantly increasing plasma insulin, hepatic glycogen, and high-density lipoprotein-cholesterol levels in an animal study. This suggests that cinnamaldehyde-A may be a potential anti-diabe. The changed plasma enzyme levels of aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, and acid phosphatase were also nearly normalized by cinnamaldehyde (Cao *et al.* 2007).

The objective of this study is to assess the in vitro antioxidant activity, acute toxicity, and dosage fixation of *C. cassia* bark in order to determine their potential therapeutic usefulness in streptozotocin-induced (STZ) mice. All of the extracts exhibit potent in vitro antioxidant activity and dose-dependent (1000, 2000, 3000, 4000, and 5000 mg/kg BW) acute toxicity in an in vivo model. Animals with the highest dose exhibited substantial elevations in the levels of aspartate transaminase (AST), alanine transaminase (ALT), base phosphatase (ALP), urea, and creatinine. STZ-treated animals (60 mg/kg BW) were followed by different doses (300, 400, and 500 mg/kg BW) of ethanol extract of *C. cassia* stem bark and glibenclamide (3 mg) in a subsequent study along with histopathological studies. The findings may provide scientific evidence for the use of *C. cassia* bark ethanol extract in traditional medicine for the treatment of diabetes and its complications. (Vijayakumar *et al.* 2022).

In this work, the bark of *C. cassia* was extracted with methanol, ethanol, and acetone, and its antioxidant activity was evaluated using 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2-azino-bis-3-ethylbenzothiazole-6-sulphonic acid. (ABTS) assays. As directed by the Organization for Economic Cooperation and Development, the acute toxic impact of *C. cassia* methanol extract (MECC) was investigated. Using diabetic mice caused by streptozotocin (STZ), the antidiabetic effects of MECC were investigated. The outcomes achieved In the DPPH and ABTS free radical scavenging tests, methanol and ethanol extracts demonstrated free radical scavenging activity. In the acute toxicity test, MECC did not exhibit significant toxic effects up to 2000 mg/kg; thus, the antidiabetic efficacy of MECC was evaluated at doses of 125, 250, and 500 mg/kg. MECC demonstrated anti-diabetic activity beginning in the second week of the experiment. MECC reduced STZ-induced hyperlipidemia in diabetic mice. Histopathological examination of liver, pancreatic, and kidney tissue sections from diabetic animals and animals treated with 500 mg/kg MECC revealed mild to moderate toxicity. MECC had notable antioxidant and anti-diabetic effects (Singh *et al.* 2018).

4 CONCLUSION

This systematic review demonstrated that cassia cinnamon has a significant effect on lowering blood glucose.

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The relationship between middle ear impairment and language development in children with Down syndrome

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ABSTRACT: Background: Down syndrome (DS) is a trisomy disorder of chromosome 21. Hearing impairment in DS is related to anatomical alterations and general cognitive delays. Otitis media with effusion is one of the most common ear problems in DS. Anatomical abnormalities and incidence of otitis media may also influence the development of their language. People with DS who have intellectual disabilities remain vulnerable to these complications and are at risk for language learning deficits. Objectives: To analyze the relationship between middle ear function and its problem with language development in children with DS. Methods: We measured the development screening and tympanometry in 17 children with DS. The study was conducted between March and July 2022 at the Pediatric and ENT clinic, Dr. Moewardi General Hospital Surakarta, Indonesia. Results: The mean age of subjects was 35.41 ± 18.78 months ranging from 12–73 months. Development delays were found in all subjects based on Denver II, 6 (35.3%) were late and 11 (65.7) were very late. Most subjects had type B for tympanometry in both ears (41.17%). Chi-Square Test between Tympanometry and Language Development was found to be significant ($p = 0.011$). Conclusion: There is a relationship between middle ear impairment and language development in children with Down syndrome.

1 INTRODUCTION

1.1 Background

Down Syndrome (DS) is the most common chromosomal abnormality found in infants and is the most common genetic disorder causing intellectual delay worldwide (Vičić *et al.* 2017). According to the Indonesian Central Agency on Statistics, the prevalence of DS aged 24–59 months was 0.13% in 2013, placing Down syndrome as the third highest prevalence of disability after the blind and speech impaired in Indonesia (Diono 2014).

Ear abnormalities are one of the most common problems in DS and can delay their developmental potential. Various previous studies reported that the prevalence of hearing loss in DS was around 36%–79% (Lau *et al.* 2015; Tedeschi *et al.* 2015) where conductive hearing loss was most common in DS (Nightengale *et al.* 2017; Phelan *et al.* 2016). Otitis media effusion (OME) is one of the most common ear problems in DS, reported to reach 93% at 1 year of age and 68% at 5 years of age (Ghadersohi *et al.* 2018; Lau *et al.* 2015). There are many reasons, especially middle ear problems related to poor prognosis of OME in Down syndrome. Anatomical differences, such as stenosis and collapse of the Eustachian tube, followed by mid-facial hypoplasia lead to a relatively small post-nasal space, and ultimately can lead to Eustachian tube dysfunction (Nogaki *et al.* 2020). The widespread hypotonia in DS causes decreased function of the tensor veli palatini, thus making

Eustachian tube opening is ineffective. Persistent OME even occurs in DS due to recurrent acute upper respiratory tract infections caused by decreased function of T and B cells or damaged neutrophil chemotaxis (Scott *et al.* 2018).

The development of language and speech skills in DS is usually slower due to a global delay in cognitive abilities. Anatomical abnormalities and the incidence of otitis media may also affect the language development of DS, although, on the other hand, several studies have found that the incidence of otitis media has no significant effect on the language development of DS. However, DS with intellectual disabilities remain vulnerable to these complications and are at risk for language learning deficits (Laws & Hall 2014; Oliver 2012).

Research related to the relationship between middle ear problems and the language development of children with Down syndrome in Indonesia is still limited. This causes attention to screening hearing and middle ear problems in children with Down syndrome not routinely carried out so that the impact on language delay is not anticipated early. This study aims to examine the relationship between middle ear function and problems with language development in children with Down's syndrome.

2 METHODS

2.1 *Study design and subjects*

A cross-sectional study was conducted from March to July 2022 at the Otorhinolaryngology Clinic and Pediatric Clinic, Dr. Moewardi General Hospital in Surakarta, Indonesia. A total of 17 children were recruited for this study.

Subjects were diagnosed with Down syndrome with DS subjects aged 1–5 years old prior to recruitment. Subjects were excluded from the study if they had ear congenital deformities (microtia). All subjects signed informed consent and the study protocol was approved by the Research Ethics Committee at Dr. Moewardi General Hospital (No. 692/V/HREC/2022).

2.2 *Data collection*

Data collection of history and language development of children was carried out using Denver II screening by calculating the difference between the delay in language ability of children with Down syndrome. The Denver examination is carried out by interviewing the parents of children with Down syndrome by pediatric residents.

Tympanometry data were collected by Tympanometry tools (GSI Tymptstar Pro – Grason-Stadler, West, USA), that previously an otoscopy examination was carried out with Otoscope (Karlz Storz, Tuttlingen, Jerman) with children and room conditioning (sedation was used if necessary) to avoid biasing results from noise and unconditioned subjects.

2.3 *Statistical analysis*

Data were analyzed using Statistical Package for the Social Sciences (SPSS) Statistic version 25 (IBM Corporation, Armonk, NY, USA). The Chi-Square test was used to assess if there were significant relationship differences between middle ear impairment and language development in children with Down Syndrome. Statistical significance was defined as a p-value of 0.05.

3 RESULTS

3.1 *Characteristic of subjects*

Table 1 shows the characteristics of the subjects included in this study. Participants' mean ages were 35 months old and mostly equal in range for gender between male and female

(9:8). The characteristics of the mother's age when giving birth with Down syndrome showed an increasing trend with age with the most age group being above 35 years. The number of ADS who had a hearing examination before the age of 1 year was 5 subjects (29.4%). The majority of subjects in this study (52.9%) received a hearing screening at least once a year after the first examination.

Table 1. Characteristics of subjects.

Parameters	Down Syndrome Subjects (n = 17)
Age (Months)	35.41 ± 18.78
Gender	
Male	9 (52.9)
Female	8 (47.1)
Siblings of DS	
Have sibling	2 (11.8)
Mother's age when pregnant (y.o)	
16–25	1 (5.9)
26–30	2 (11.8)
31–35	6 (35.3)
> 35	8 (47.1)
First hearing screening (months)	
Never	6 (35.3)
< 6	2 (11.8)
7–12	3 (17.6)
> 12	6 (35.3)
Hearing check-up frequency	
Never	6 (35.3)
1x / year	9 (52.9)
> 1x / year	2 (11.8)
Delay of language development	17 (100)

In Table 2 it can be seen that the language development of children with Down syndrome is not in accordance with the range of normal children and tends to experience delays. The range of the results of this study is not much different from the range in previous studies

Table 2. Speech skill overview of children with Down syndrome.

Milestones	n	Range	Prior study*	Mean	Normal kid's range
Babbling	17	4–12	3–12	8.41 ± 2.72	0–3
First word	13	12–30	12–48	20.00 ± 5.43	6–9
Phrase	9	18–48	18–72	30.36 ± 11.96	12–24
Sentence	6	36–60	36–60	43.67 ± 9.16	24–36

3.2 Results of chi-square test

We performed a chi-square test to assess the relationship between middle ear impairment (i.e., tympanometry test) and delayed development of language in children with Down Syndrome. Table 3 demonstrated that the relationship between tympanometry results and language delay in Down Syndrome showed significant results ($p < 0.05$) where subjects who

had bilateral type B or type C results tended to be very late in the development of language and subjects with type A at least one ear tended to be only late in development of language.

Table 3. Tympanometry and delayed development of language.

Tympanometry	Delayed n (%)	Very delayed n (%)	p-value
Type A Bilateral	2 (33.3)	0	0.019*
Type A/B	3 (50.0)	1 (9.1)	
Type B Bilateral	1 (16.7)	6 (54.5)	
Type C Bilateral	0	4 (36.4)	

4 DISCUSSION

Advances in science have a significant impact on the lives of children with Down syndrome. The life expectancy of children with DS in America increased from only 10 years in 1960 to 47 years in 2007 (Shin *et al.* 2009). Infant mortality under 1 year decreased from 8.5% to 5% (Presson *et al.* 2013). This situation encourages scientists to focus on the quality of life of children with DS (Bull 2018; CDC 2020).

Down syndrome is characterized by a variety of dysmorphic features, congenital malformations, and other health problems and medical conditions (Ramia *et al.* 2014). The majority of children with Down syndrome suffer from otologic conditions, such as chronic otitis media and hearing loss, which call for examination and care from an otolaryngologist because they may hinder DS patients from realizing their full developmental potential (Bull *et al.* 2022).

The ratio of men and women in this study is mostly equal (9:8), quite similar to a large-scale study by Kreicher *et al.* (2018) in the USA where the ratio is 6:5. Our study showed that the mother's age when giving birth with Down syndrome had an increasing trend with age with the most age group being above 35 years. Prevalence of Down syndrome is highly dependent on the gestational timing at ascertainment and maternal age (Mai *et al.* 2020). Our data is consistent with data from the CDC, (2020) and Mai *et al.* (2020) where the DS birth rate increased sharply from <8/10,000 (maternal age <30 years) to 38/10,000 (maternal age 35–39 years) and 121/10,000 births (maternal age > 40 years). Prevalence rises from 1/1445 live births at the maternal age of 20 years to about 1/25– 1/30 at the age of 45 years. Maternal age is the most significant factor of nondisjunction trisomy 21. Approximately 75% of maternal and 50% of paternal nondisjunction occurs in meiosis I, with the remaining nondisjunction occurring in meiosis II (Korlimarla *et al.* 2021).

Our study found that there were still 35.3% of parents of children with DS who had never had their children's hearing checked and 52.9% had just had hearing screening done over the age of 1 year. This data shows that parental knowledge regarding Down syndrome is still lacking. According to the AAP recommendations 2022, objective tests should be used to conduct hearing screening in the first month following delivery to check for congenital hearing loss and behavioral audiogram and tympanometry should be carried out every six months for a child who passes diagnostic hearing testing until normal hearing levels are established bilaterally by ear-specific testing (Bull *et al.* 2022).

In this study, 15 of 17 (88.2%) children with DS had abnormal tympanometry in at least one ear. These results are in line with previous studies regarding the vulnerability of children with DS to problems in the middle ear (Nogaki *et al.* 2020; Scott *et al.* 2018). DS patients frequently have structural issues that put them at risk for conductive hearing loss, and it should be noted that children with Down syndrome frequently develop OME. (Hargunani *et al.* 2020; Scott *et al.* 2018)

The relationship between tympanometry results and language delay in Down Syndrome showed significant results ($p < 0.05$) where subjects who had bilateral type B or type C results tended to be very late in the development of language and subjects with type A at least one ear tended to be only late in the development of language. Otologic treatment, including placement of pressure equalization tubes, is the first step to improving the hearing and developmental outcomes of many of them. Due to the risk of HL in these patients and the significant benefit patients gain from early intervention for hearing loss, it is imperative to avoid diagnostic delays (Nightengale 2018).

For children with DS who are intellectually challenged due to mental retardation, the hearing loss may cause even further cognitive development delay (Bull *et al.* 2022). Down syndrome the development of language is not suitable for normal children. Children with DS demonstrate particular deficits in speech and language development and they have significantly higher rates of articulatory impairments when compared with other children. Difficulty in perceiving and producing speech results from neurological development of language, language learning environment, hearing loss, subtypes of DS, motor coordination and timing deficit, and orofacial characteristics (Ramia *et al.* 2014). At an early stage, language is acquired in a pattern similar to, but delayed, when compared with typically developing children with equivalent mental ages. Babbling is often delayed, has a different quality, and continues to occur over a more prolonged period. In several areas related to speech/language development, the level of impairment is greater than expected for overall mental age (Korlimarla *et al.* 2021).

5 CONCLUSION

There is a relationship between middle ear impairment and language development in children with Down syndrome which is disorders of the middle ear tend to slow down the development of language skills in children with Down syndrome. The limitation of this study was not categorizing Down syndrome in more detail where Down syndrome has different genotype mosaic levels which will affect the phenotype of the child and both the condition of their ears and their language development potential.

ACKNOWLEDGMENTS

Universitas Sebelas Maret in Surakarta, Indonesia fully financed this initiative.

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The shrimp skin extract (*Litopenaeus vannamei*) as an adjunct therapy of hemostasis in open fracture

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ABSTRACT: Shrimp is the main export commodity of Indonesian fisheries. The majority of shipments are in the form of fresh frozen shell-less shrimp, which results in increased shrimp shell waste. The utilization of waste is still lacking even though shrimp shells have many important ingredients, one of which is chitosan. Chitosan has been shown to be able to accelerate hemostasis. The aim of this study to examine the shrimp skin extract as an adjunct therapy of hemostasis in hemostasis through a clotting time (CT) test in open fracture. This study was an experimental study with 18 *Rattus norvegicus* induced by fracture, divided into 3 groups, control, oral chitosan, and topical chitosan. The control group did not receive chitosan therapy, but all groups received levofloxacin injection and splint dressing. The clotting time test using the Lee-White method was held on days 1, 3, and 5 by taking venous blood through the orbital sinus, for each clotting time test, 2 samples were taken from each group and euthanized immediately after blood collection. The data obtained were analyzed using Kruskal-Wallis. The results showed that there was a decrease in CT time although it was not statistically significant in the CT test on day 1 ($p = 0.156$), day 3 ($p = 0.102$), and day 5 ($p = 0.368$). There were a significant improvement in swelling found in the topical chitosan group. There was no significant difference in the clotting time test in the three groups. There was an improvement in swelling in the group given topical chitosan compared to the control group and the group given oral chitosan. There was an accelerated onset of hemostasis (clotting time) in the group receiving topical chitosan.

1 INTRODUCTION

Exports of Indonesian fishery commodities are highly dependent on two main types of commodities, namely shrimp and marine fish groups such as skipjack tuna and tuna. Shrimp commodity is still a leading commodity with a total of 34.83% of the total export value which reached USD 4.94 billion as of December 2019. Shrimp is exported in the form of fresh frozen shrimp, which has undergone cold storage after going through the separation of the head and skin which produces industrial waste of 25% of the total production with the utilization of waste only 30% (Kementrian Kelautan dan Perikanan 2020).

Nowadays, shrimp waste has only been used as raw material for the food industry, animal feed, and agriculture, but the amount used is only 30% of the existing waste (Kementrian Kelautan dan Perikanan 2017). Waste treatment that is less than optimal causes environmental pollution, especially odors and poor environmental aesthetics. If it can be managed properly, chemical treatment of demineralization and deproteinization of dried shrimp shell waste can produce chitin which is the most abundant natural polymer in the world after cellulose. The reaction of removing the acetyl group in chitin is a process of transforming chitin into chitosan compounds. Chitosan, dubbed the magic of nature (Lee 2004), can be

used in food processing, medicine, biotechnology and is an attractive material in biomedical and pharmaceutical applications (Dompeipen *et al.* 2016).

Chitosan is widely used in the medical field because it has the ability as a hemostatic agent. As a hemostatic agent, chitosan activates and initiates platelet adhesion and aggregation, thereby accelerating the formation of blood clots, which is the most crucial phase in emergency trauma (Hu *et al.* 2018). One form of emergency trauma that most utilizes chitosan as a hemostatic agent is fracture trauma. A fracture is a break in the continuity of bone and or cartilage tissue which is mostly caused by forced trauma (Sjamsuhidayat 2007). It makes this type of fracture the most life-threatening and requires immediate help is an open fracture. In open fractures, there are 5 important things that need attention, such as, bleeding, possible infection, the disproportionate strain between the fragments, hypoxia in the bone, and inability to bear. Post-traumatic uncontrolled bleeding is still the leading cause of avoidable death in trauma patients whereas one-third of trauma patients present to the hospital with signs of coagulopathy (Baker *et al.* 2018). The addition of chitosan in bleeding patients can help primary hemostasis by faster blood clot formation (Spahn *et al.* 2019).

Fractures have proven to increase blood coagulation in rabbits several days after the fracture occurs (Kunio *et al.* 2013). This is a form of compensation for the body not to lose more blood. The addition of chitosan therapy in fracture management is expected to accelerate blood clotting in patients to get maximum results. Hemostasis is compensation for bleeding, where in the first 5 minutes there is primary hemostasis which is compensation for endothelial damage that causes platelets to adhere to exposed collagen, forming platelet plaques (Li *et al.* 2013). In addition to hemostasis, cellular reactions, vascular reactions also occur are initiated by reflective vasoconstriction and then maintained by local factors such as epinephrine and 5 hydroxy tryptamines (Oesman & Setiabudy 2009). Hemostasis product innovation has begun to develop to create more effective products, such as gauze containing chitosan grains (Spahn *et al.* 2019).

In general, these chitosan-based products work by affecting the independent coagulation pathway or commonly known as the extrinsic pathway (Benesch & Tengvall 2002; Rao & Sharma 1997; Shafer *et al.* 2015). Several studies have shown that chitosan can activate and initiate platelet adhesion and aggregation which is a crucial phase in hemostasis and wound healing (Thatte *et al.* 2004). This occurs due to the interaction of electron bonds on the surface of chitosan. This interaction accelerates the formation of blood clots or thrombus (Chou *et al.* 2003). The effect of administration of crustacean shell extract on hemostasis in open fractures is still unclear. Research on chitosan is still mostly using samples on teeth and other oral organs, where there is still little that discusses the use of chitosan in long bones and surrounding tissues. Until now, research on chitosan in long bone fractures has focused more on its benefits as a bone remodeling agent, where chitosan can initiate growth factor molecules to the injured area and can form a layer with a good density level. Whereas in this process, electron interactions also occur on the surface of chitosan which causes the ability to bond between cells between membranes which is a hemostatic biomaterial. Research on its effect on hemostasis has not been done much, even though in the case of emergency trauma, in this case an open fracture, control bleeding is the most vital thing that must be considered because it can lead to shock. The crustacean shell has the potential to be developed as a supportive therapy for stopping bleeding. It is necessary to carry out biomolecular research related to this so that there is scientific evidence.

2 MATERIAL AND METHODS

The study was approved by Health Research Ethics Committee of FKIK UMY with Ethical Approval Number 13/EC-KEPK FKIK UMY/II/2021. This study was an experimental study, posttest control design. The subjects were 18 rats (*Rattus norvegicus*) Wistar strain divided into 3 groups (control, oral chitosan, and topical chitosan). The inclusion criteria of subjects were determined, such as, male rats aged three months, healthy, and weighing

200–250 grams. Rats were given staple food in the form of A594K pellets and drinks using water ad libitum. Lighting is given 12 hours of light and 12 hours of darkness. The temperature is set in a temperature range of 25°C – 30°C with good air circulation, using a fan. The lighting in cage is given 12 hours of light and 12 hours of darkness. Rats will be excluded if they die before the time of observation.

An open fracture in the study subject was induced using a saw on the tibia. This open fracture will cause the bone to open and damage to the overlying fascia such as the periosteum, skeletal muscle, sub cutis, and cutis. Clotting time testing using the Lee-White method with test tubes that were immersed in a water bath at a temperature of 37°C. The time calculation starts with the first time the blood touches the tube and stops until the blood clots where if the tube behind the blood is no longer spilled. The blood taken is venous blood through the orbital sinus. The 18 mice used in this study were divided into three groups, namely a control group without chitosan therapy (control), a group with additional topical chitosan therapy (topical), and a group with additional oral chitosan therapy (oral). All three groups were manually induced fracture in the tibia.

Extraction of chitosan was obtained from shrimp shell powder which went through a deproteination process that began with immersion in 3.5% NaOH (1:10 ratio) for 2 hours in a water bath with a temperature of 65°C, then filtered and washed the precipitate until it reached a neutral pH. Then in the oven to dry. The demineralization process is immersion of the dry deproteination product with 1N HCl (1:15 ratio) for 1 hour in a water bath at 60°C, followed by drying at 60°C. The dried product was soaked with 0.315% NaOCl (1:10 ratio) in a water bath for 1 hour at 40°C followed by drying to produce chitin compounds. The change of chitin into chitosan must go through a deacetylation process, namely, by immersing it using 60% NaOH (1:20 ratio) in a water bath for 1 hour at a temperature of 60°C followed by drying (Dompeipen *et al.* 2016).

2.1 Statistical analysis

Data analysis using Kruskal-Wallis, with a significant limit value of $p < 0.05$ with a 95% confidence interval.

3 RESULTS AND DISCUSSION

The clotting was measured using the Lee-White method. The result showed the control group was 384.67 ± 168.34 seconds, the group with additional oral chitosan therapy was 391.83 ± 90.80 seconds, the group with additional topical chitosan therapy was 306.16 ± 19.28 seconds. The data showed a shortened clotting time in the group of rats receiving additional chitosan therapy, especially in the group with topical administration (Table 1).

Table 1. Clotting time.

Groups*	Clotting Time (average) (seconds)			Maximum (seconds)	Minimum (seconds)	Average \pm SD (seconds)
	Day 1	Day 3	Day 5			
Control	498	476.5	179.5	535	106	384.67 ± 168.34
Oral**	475.5	399	301	512	244	391.83 ± 90.80
Topical**	312.5	319	287	329	285	306.16 ± 19.28
Kruskal-Wallis Test	$p = 0.156$	$p = 0.102$	$p = 0.368$			

*all groups were induced fracture

**groups with additional therapy of chitosan

The results of the analysis test showed that the results were not significant, which means that there was no significant difference in the change in clotting time in all groups on the day of data collection. However, there is a difference in the swelling conditions around the lesion, which can be seen in the image below.

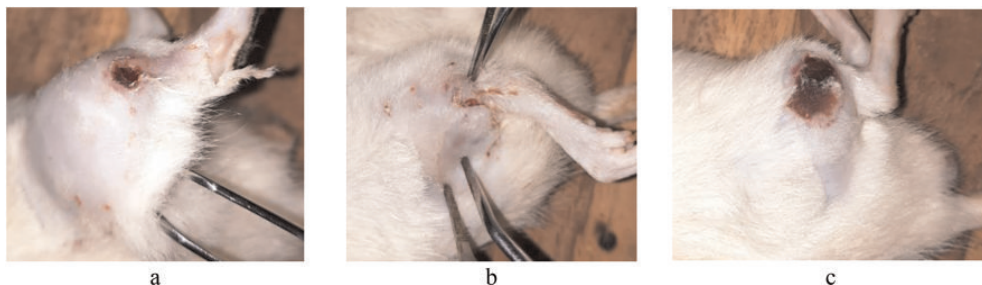


Figure 1. a) wound in control group; b) wound in topical group; c) wound in oral group.

The condition of the wound around the fracture showed improvement significant in the topical group. Figures 1b shows the minimum swelling compared to Figures 1a and 1c. This shows the formation of a thrombus (blood clot) which is the main result of primary hemostasis forming better and faster in the topical group. The success of hemostasis in the addition of chitosan therapy is not only enough to be seen from the significant value of clotting time but can also be seen from the conditions around the wound.

4 DISCUSSION

This study aims to examine shrimp shell extract as an adjunctive therapy for hemostasis in hemostasis through the coagulation time (CT) test in open fractures. The results of this study showed that there was no significant difference in the freezing time test in the three groups. There was an acceleration of hemostasis (clotting time) in the group that received topical chitosan. According to research conducted by Win (2016), the average clotting time in healthy white male rats was 4 minutes 51 seconds. If we take a look at table three, the results of the clotting time on the first day in the control and oral groups showed that the clotting time was far above normal. According to The European guidelines on the management of major bleeding and coagulopathy following trauma (Baker *et al.* 2018), prolongation of clotting time is common in the early onset of bleeding cases. In bleeding, hypoperfusion occurs, reduced clotting factors, acidemia, hypothermia, and dilution can cause endothelial dysfunction. The progress of endothelial dysfunction will worsen in cases of uncontrolled bleeding, which will result in coagulopathy. However, in controlled bleeding such as in the current study, in the third table in the control group, there was a shortening of the clotting time, which indicates well-compensated hemostasis.

Research by Li *et al.* (2013), showed an increase in blood coagulation on day 1 and day 5 in rabbits induced by fracture. This is in line with the results of this study, wherein in all groups, there was an increase in blood clotting. What is interesting is that in the group given topical chitosan, the clotting time on the first day directly matched the clotting time in normal rats (without fracture). Whereas in the control and oral groups it can only be achieved on day 5. From here we can see the effect of chitosan with topical administration can accelerate hemostasis compensation in the body. In the control group, there was an increase in CT time from day to day. Although on the first day there was a big difference

with the topical chitosan group, on the fifth day, the three groups had close CT times. Where the increase in CT in the control group is by the study conducted by Li *et al.* (2013), showed an increase in thrombin time (TT), fiber fibrinogen (FIB), and D-dimer (DD) on the first day after fracture surgery and an increase in activated partial thromboplastin time (APTT), TT, FIB, and DD on the fifth day. after fracture surgery. This study was conducted on rabbits with induced fracture. Researchers conducted a blood clotting test which was simpler, namely by clotting time. Although the results that the researchers got were not significant, they showed that there was indeed an increase in post-fracture blood coagulation. Differences in final results can be caused by different research samples, stress, and other factors.

This study showed similar results to the control. Even the mean CT on the last day was still slightly higher for the control group. Research on the administration of chitosan extract orally is still rarely done. There are several similar studies, but the discussion is its effect on alveolar bone density after tooth extraction. Based on the results of the clotting time, it can be seen that oral administration of chitosan did not give significant results. This is due to the low pharmacokinetics of chitosan orally in the body. Based on the research of Li *et al.* (2015) showed that only 20% of chitosan was detected while the rest could not be detected. The degradation products of chitosan itself are found in the liver and kidneys. Because of this, the oral administration of chitosan is not effective because it will not reach the target lesion (Win 2016). Based on research by Sari *et al.* (2019), regarding the effect of chitosan on hemostasis in vitro, it was explained that chitosan gradually depolymerizes the release of N-acetyl-D-glucosamine which will initiate primary hemostasis using fibroblast proliferation and accelerated collagen deposition in the wound area which will accelerate the formation of fibroblasts. The theory of chitosan increasing hemostasis can still be proven in this study, by seeing the improvement of swelling around the wound. Swelling in the case of third-degree open fractures is very common considering that swelling is a manifestation of the formation of a hematoma in the tissue due to damage to blood vessels (Li *et al.* 2015; Nabila & Indriawati, 2021). A comparison of the difference in swelling around the wound in the 3 groups (Figure 1). It shows that the acceleration of clotting time from day one can significantly create temporary blockage in damaged blood vessels, thereby preventing the formation of excessive hematomas in the tissues. The results of the research are in accordance with the research conducted by Kunio *et al.* (2013) increased swelling. This shows that the blood clot formed well in the blood vessels of the chitosan group which was given topically.

5 CONCLUSION

There was no significant difference in the clotting time test in the three groups. There was an improvement in swelling in the group given topical chitosan compared to the control group and the group given oral chitosan. There was an accelerated onset of hemostasis (clotting time) in the group receiving topical chitosan.

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The cardioprotective effect of Thymoquinone in Lipopolysaccharide-induced Sprague Dawley Mice (LPS: Induction study of an acute myocardial infarction model)

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ABSTRACT: Myocardial infarct induction in rat models with isoproterenol is a standard in cardioprotective research on various test substances. The other myocardial infarct induction model uses Lipopolysaccharide (LPS). LPS and isoproterenol show the same induction mechanism on myocardial damage, that is disturbed balance in free radical formation and antioxidative resistance system. This research aims to examine the difference between LPS and Isoproterenol injections in rat models by fibrosis area. This research used a posttest-only control group design with 15 Sprague Dawley rats as samples which were divided into four groups: NaCl control group, LPS 10 mg/mL group, LPS 15 mg/mL group, and isoproterenol group. The LPS and isoproterenol groups were respectively given intraperitoneal injection with LPS and isoproterenol for 14 days, while the control group was not given any treatment. On day 15, they were terminated and measured histopathologically for fibrosis area using a micrometer. This research showed that the groups administered with LPS 10 mg/mL and 15 mg/mL resulted in myocardial infarcts of $51.910 \mu\text{m}^2$ and $102.512 \mu\text{m}^2$, respectively, while the group administered with isoproterenol resulted in myocardial infarct of $21.190 \mu\text{m}^2$. This research showed that LPS 15mg/mL induction is relevant for the development of animal models with Acute Myocardial Infarction.

Keywords: Acute Myocardial Infarction, Lipopolysaccharide, Isoproterenol

1 INTRODUCTION

Cardiovascular disease is a primary cause of death globally. According to WHO, about 17.9 million people died because of cardiovascular disease in 2019, representing 32% of all

deaths globally (WHO 2021). Acute myocardial infarction is one part of coronary heart disease which is a cardiovascular problem with high hospitalization and death rates (Simanungkalit & Supit 2022). Global epidemiological research data showed that 126 million people were affected by acute myocardial infarction in 2017 (Simanungkalit & Supit 2022).

The model of myocardial infarct induction on experimental animals has been performed through several methods. Some induction methods tried on animals used chemicals, open surgery, or closed catheter methods (Halim *et al.* 2018). One of the chemical induction methods commonly used in cardioprotective effect research is isoproterenol. Widyaningsih *et al.* showed that isoproterenol administered at a dose of 85 mg/kg BW for two days consecutively caused acute myocardial infarction as shown with change in EKG image as marked with an elevation on ST segment that is a distinctive image feature of acute myocardial infarct in the group of rats given with isoproterenol. Morphologically, isoproterenol administration caused a macroscopic change in the rats' hearts with the white ventricular area, showing an ischemic area in the heart. Macroscopic heart change in the left ventricular area was confirmed through dying using TTC on the left ventricular area, which was myocardial necrosis, as marked with cardiac muscle cells having pyknosis (karyopcnosis), muscle fiber getting smaller, space between muscle fibers getting larger and neutrophil infiltration (Widyaningsih 2015).

The chemical in the chemical induction method for myocardial infarction other than isoproterenol that is not commonly used in research is lipopolysaccharide (LPS). LPS is a main constituent endotoxin from bacterial cell walls commonly used to induce immune response and septic response. LPS administration may induce myocardial damage through the overproduction of auto-oxidized cytotoxic free radicals. LPS exposure in experimental animals is reported to cause stress on cardiomyocytes causing loss of myocardial integrity due to oxygen deficiency, calcium overload, and overproduction of free radicals (Xu *et al.* 2018).

LPS and isoproterenol administrations show similar intermediate myocardial damage induction mechanisms, disturbing the balance between free radical formation and anti-oxidative resistance system (Xu *et al.* 2018). The difference between the two in the change in cardiac histopathological image is not really known. This research aimed to examine the difference in LPS and Isoproterenol injections in a rat model by fibrosis area as measured histopathologically using a micrometer.

2 METHODS

This experimental research used a post-test-only control group design. The research samples were Sprague Dawley rats that were kept at IBL Laboratory, FK, Unissula Semarang. Fifteen Sprague Dawley rats were divided into five groups, thus three rats in each group: NaCl control group; LPS 10 mg/mL group; LPS 15 mg/mL group; and Isoproterenol group. For 14 consecutive days, the rats in LPS groups were given intraperitoneal injections of LPS, rats in the control group were not given any treatment, and rats in the Isoproterenol group were given intraperitoneal injections of Isoproterenol. On day 15, they were terminated through chloroform inhalation and sampled for serum and heart organs, which were fixated using bouin solution.

The experimental animals were dissected and their hearts were taken. The heart organs were made into histopathological preparations using Masson's Trichrome dying by an anatomical pathologist. Preparations were read under a binocular microscope (40× magnification). Five fields of view were taken on apex-to-basics cut and counted for a blue area on the perivascular area and myocardial tissue. The fibrosis area was measured using a

micrometer. Histopathological preparations were read by two anatomical pathologists at separate places.

The data were analyzed using Saphiro-Wilk's normality test and Levene's homogeneity test. One Way Anova test was conducted to examine the difference between treatments and whether the data were normal and homogenous, and the Kruskal-Wallis test was conducted to examine whether the data were not distributed normally or homogeneously. The data were analyzed using SPSS application version 25. The test result was considered significant if $p < 0.05$.

3 RESULTS

Saphiro-Wilk's normality test on the treatment groups showed normal data distribution ($p > 0.05$). The results of Levene's statistic homogenous test showed non-homogenous data distribution with a significant value $p = 0.021$ ($p < 0.05$). Kruskal-Wallis test of non-parametric statistical analysis was conducted since the data did not meet the homogeneity assumption.

As shown in Figures 1 and 2, the infarcts arising in LPS 10mg/mL and 15mg/mL groups were $51.910 \mu\text{m}^2$ and $102.512 \mu\text{m}^2$. Meanwhile, Isoproterenol injection caused a narrower myocardial infarct of $21.190 \mu\text{m}^2$.

Based on the examination of troponin levels in the four groups (Figure 3), isoproterenol group had the highest troponin level of 9.26 ng/dL, while the control group had the lowest troponin level of 7.79 ng/dL.

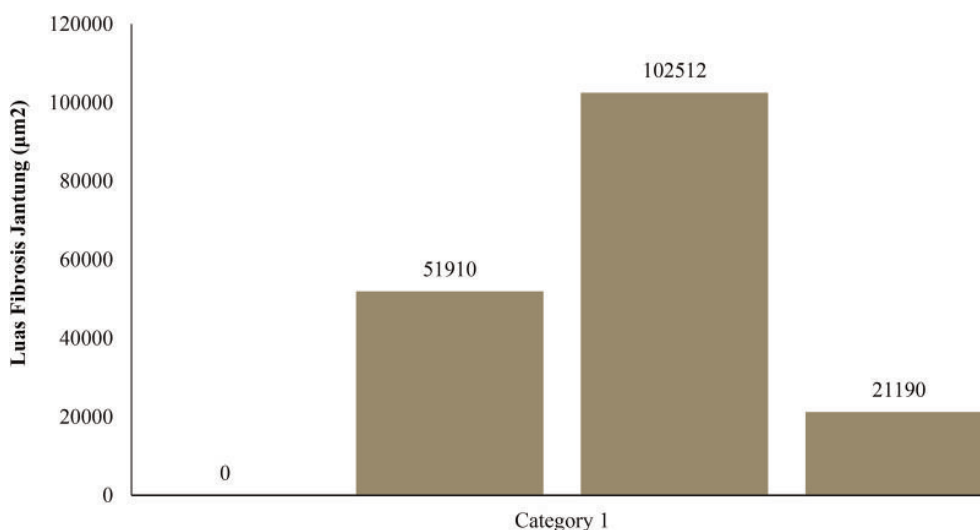


Figure 1. Comparison of cardiac fibrosis areas. ISO = Isoproterenol.

Based on the Kruskal-Wallis test results, there was no significant difference between the treatment groups in fibrosis areas at significance value $p = 0.077$ ($p > 0.05$).

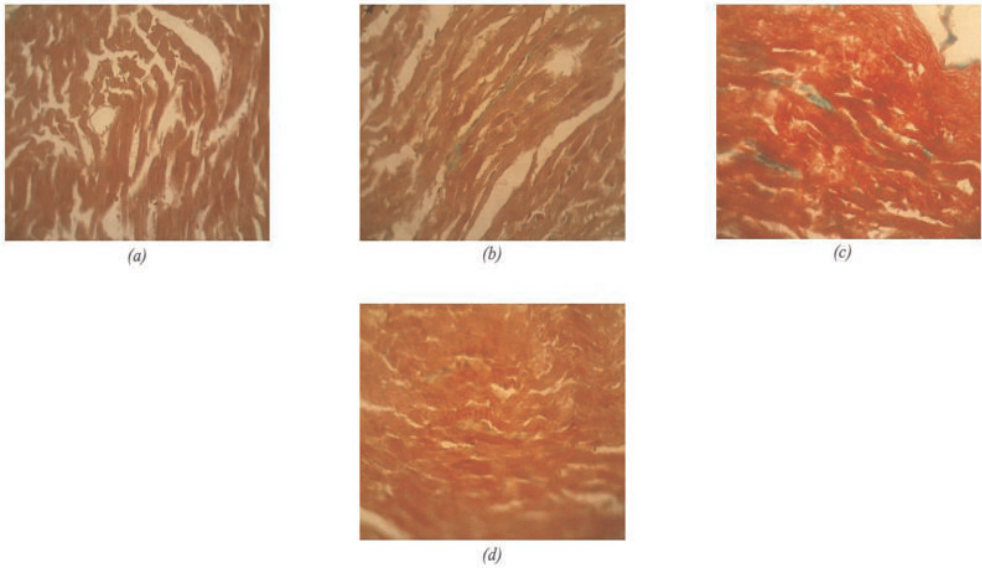


Figure 2. Histopathology of rat's heart (40× objective magnification) Fibrosis areas of groups: (a) NaCl control, (b) LPS 10, (c) LPS 15, (d) Isoproterenol.

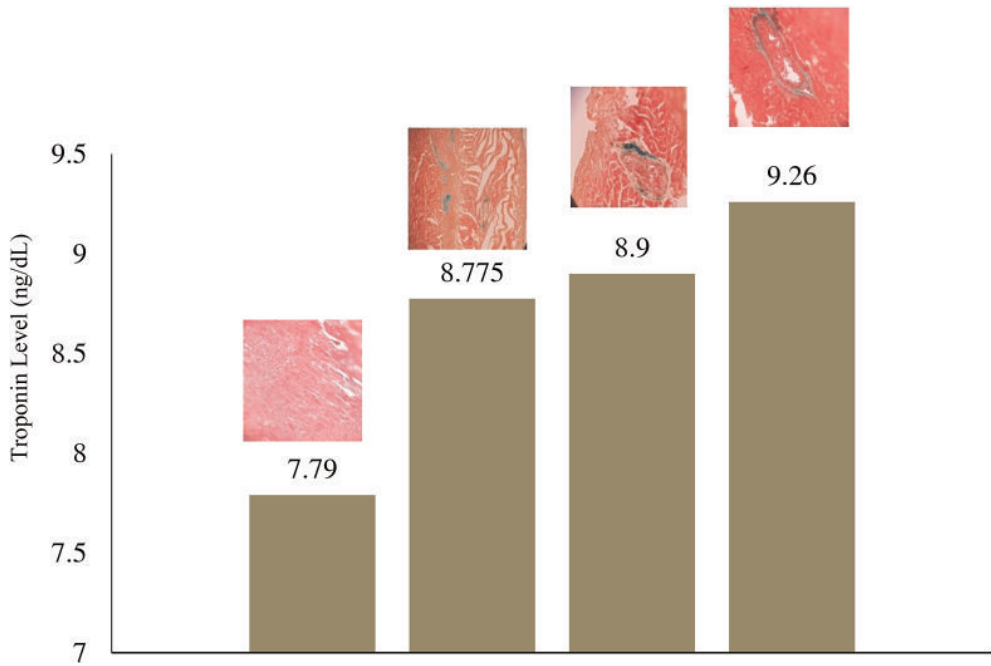


Figure 3. Troponin level in treatment groups.

4 DISCUSSION

This research shows that LPS injections at doses 10 mg/mL and 15 mg/mL and Isoproterenol induced fibrotic reaction in myocardium. LPS groups administered at doses of 10 mg/mL and 15 mg/mL had wider histopathological images of the fibrosis area than the isoproterenol group. This result conforms to the study conducted by Asgharzadeh *et al.* that there is fibrosis in rat's heart induced with LPS (Asgharzadeh *et al.* 2018). LPS administration in the rat model compared with the control group in previous studies evidently caused a significant increase in histopathological change in collagen deposition on the left ventricular wall (Asgharzadeh *et al.* 2018). The research conducted by Huang *et al.* showed that LPS administration at a dose of 10 mg/kg for 2 weeks could induce fibrosis model in male C57BL/6 mice (Huang *et al.* 2018).

Previous studies stated that LPS served as a bacterial endotoxin, which was a component from the outer membrane of Gram-negative bacteremia, and was deemed as the main cause responsible for heart dysfunction in sepsis (Bai *et al.* 2016). Mechanically, LPS is associated with Toll-Like-Receptor 4 (TLR4) with the assistance of LPS binding protein CD14 which then produces inflammatory cytokines, such as TNF α , IL-1 β , and IL-18, which may directly cause heart dysfunction (Tan *et al.* 2018; Weis *et al.* 2017; Zhang *et al.* 2017). The mechanism by which LPS can cause myocardial infarction is mediated by oxidative stress (Kallapura *et al.* 2014; Neri *et al.* 2016; Su *et al.* 2018). LPS exposure may trigger prolonged production of inflammatory mediators and may cause destructive conditions and oxidative stress due to excessive production of these radicals, related to inflammatory conditions (Kallapura *et al.* 2014).

This research result shows that Isoproterenol administration to experimental animals may cause myocardial fibrosis, even with a smaller fibrosis area than the LPS groups. Isoproterenol is a synthetic sympathomimetic catecholamines and β -adrenergic agonist that produces 'infarct-like' myocardial necrosis similar to myocardial infarct in humans (Halim *et al.* 2018). Isoproterenol works non-selectively on receptors β 1 and β 2. Receptor β 1 is mainly expressed in the heart, thus its stimulation causes positive chronotropic, dromotropic, and inotropic effects (Halim *et al.* 2018). Previous studies reported that isoproterenol mechanism-induced myocardial infarction is hypoxia due to myocardial hyperactivity and reduced tension in coronary artery, and free radical production due to catecholamine auto-oxidation that caused membrane peroxidation (Ahsan *et al.* 2020).

This research result conforms to the theory that β -adrenergic receptor (Isoproterenol) stimulation may produce reactive oxygen species (ROS) and cause an imbalance between free radical production and antioxidative resistance mechanism (Hosseini & Rajabian 2022; Mohan *et al.* 2019). Myocardial infarction induced with Isoproterenol has been documented in many researches on experimental animals with manifestations similar to those found in humans (Huang *et al.* 2018; Yehia *et al.* 2021; Zaafan *et al.* 2013).

5 CONCLUSION

LPS induction at a dose of 15 mg/mL causes wider myocardial fibrosis in Sprague-Dawley rats than LPS induction at a dose of 10 mg/mL and isoproterenol induction. Further research is needed on different models for inflammatory induction, especially in chronic conditions, for agreement on this research's findings and for appropriate mechanisms of fibrosis-induced inflammation.

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Analysis of flavonoid ceciwis cabbage (*Brassica oleracea* var. *capitata alba*) as an immunomodulator with maceration method

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ABSTRACT: Free radical formation and oxidation reactions in biomolecules will last throughout life. This oxidation process can result in the production of extremely active free radicals that can harm the cellular structure and function. But the activity of these free radicals can be inhibited by antioxidants that complement the immune system. However, the lack of publication makes only a small percentage of the public know what local foods contain flavonoids such as fresh cabbage. The making of the extract is preceded by the treatment of opening the pores on fresh cabbage ceciwis using Microwave Assisted Extraction (MAE) for 5 minutes, then soaked with 70% ethanol with a 1:10 compared. Extracts that have been obtained are tested flavonoids using UV-Vis spectra. The maximum wavelength is obtained at 415 with an absorbance of 0.723. The total value of flavonoid ceciwis cabbage method of maceration by 1.1045% and maceration with MAE treatment by 2.5072%. The results showed the potential of cabbage ceciwis as an immunomodulator with the method of maceration of mae initial treatment better than without initial treatment.

1 INTRODUCTION

Free radicals are constantly forming in the body. Most are thought to be involved in various degenerative disease processes (Halliwell 2012). Radical compounds damage cells causing diseases such as liver, cancer, and age-related conditions such as Alzheimer's (Rahardjo *et al.* 2006). Free radical formation and oxidation reactions in biomolecules will last throughout life. This oxidation process can result in the production of extremely active free radicals that can harm the cellular structure and function. But the activity of free radicals can be inhibited by antioxidants that complement the immune system (Sen & Chakraborty 2011).

Antioxidants are chemical compounds that at low concentrations can significantly prevent substrate oxidation in chain reactions. Antioxidants have the capacity to shield cells from the harm wrought by free radicals. Beta-carotene, lycopene, vitamin C, vitamin E, and flavonoids are a few examples of antioxidants. Flavonoids are organic antioxidants that are present in a variety of foods, including whole grains, fruits, vegetables, and animals. Natural antioxidants are currently considered to be one of the essential alternatives due to worries about the potential for unidentified adverse effects of synthetic antioxidants. In Indonesia, there are many local food ingredients that can be used as a source of natural antioxidants. However, the lack of publication makes only a small percentage of the public know what local foods contain flavonoids such as fresh cabbage (Inggrid & Santoso 2014).

Vitamins (A, C, E, thiamine, riboflavin, nicotinamide), calcium, and beta carotene are all present in fresh cabbage along with water, protein, fat, carbs, fiber, calcium, phosphorus,

iron, salt, and potassium. Additionally, it contains iberine, sulforaphane, and compound sianohidroksibutene (CHB), which promote glutathione. Additionally, cabbage plants have long been used as a cure for itchiness caused by the *Candida* (candidiasis) fungus, fungal-skinned hands, feet, excessive blood cholesterol levels, and arthritis (arthritis), Antidote in alcohol intoxication (hangover), toxins in the heart, difficulty defecating, preventing enlarged tumors, and increasing breast milk production.

Fruits and vegetables, as well as nuts, seeds, tea, and other food products, all contain natural antioxidants (Silvia *et al.* 2016). A recent study explained that plant-based food products generally have a higher antioxidant content than animal food products. One of the vegetables that contain anti-oxidants is cabbage, which will be used in this study the end is commonly called *cuciwis* or *ciwis* with testing on the determination of flavonoid levels (Sen & Chakraborty 2011).

The method of withdrawal of flavonoid compounds is very influential on the results of the content obtained. The greater the content of the compound obtained, the potential as an immunomodulator will be better.

2 MATERIALS AND METHODS

This study was carried out in the lab of DIII Pharmacy Polytechnic Harapan along with the materials used including cabbage *ceciwis*, ethanol, methanol, kuarsetin (raw curve). As for the tools used analytically, knives, telenan, spoons, label paper, sample containers, filter paper, maceration tools, stirrer rods, erlenmeyer, measuring cups, funnels, mortars, stamfers, blenders, microwaves, rotary evaporators, uv-vis spectrophotometry.

2.1 *Material processing*

In the processing of materials begins with the collection of raw materials. At this stage each material is made in powder. The preparation of making powders include the following:

2.1.1 *Selection of raw materials*

This stage of raw material selection is adjusted to a good harvesting time. The sample is selected in a fresh state, so that the content of secondary metabolites contained in it can be digested properly.

2.1.2 *Wet sorting*

At this stage after each material is collected then selected and separated from the impurities such as roots, soil and others.

2.1.3 *Washing*

This washing is intended to clean raw materials from impurities, namely by using running water (Nurhasnawati *et al.* 2017).

2.2 *Extract making*

Extract is made in two ways, namely by direct and indirect maceration by the treatment of the opening of pores first (Kuntorini *et al.* 2018).

2.2.1 *Opening of pores*

Fresh samples are put into MAE, then set the power by 100watt for 2 minutes. Take a sample from MAE and then macerate it with a solvent ratio of 1:10 for 5 days. Steam until you get a thick extract.

2.2.2 *Flavonoid qualitative test*

The extract of 0.5 grams 2 mL of 70% ethanol is added, followed by the addition of 3 drops of concentrated HCl, 0.5 grams of magnesium powder, and stirring. When orange turns to red, it means.

2.2.3 *Flavonoid quantitative test*

2.2.3.1 *Manufacture of quercetin master solution*

Weighed 20 mg of quercetin dissolved to a mark in a 50 mL measuring jug using a 96% ethanol solvent (400 ppm).

2.2.3.2 *Concentration series creation*

Made series concentration from the parent solution 400 ppm by means of the parent solution 0.5 mL; 1.25 mL; 0.75 mL; 0.85 mL is inserted into the pumpkin takar and added ethanol up to 50 mL so that the raw solution concentration is obtained 40 ppm, 50 ppm, 60 ppm, 70 ppm.

2.2.3.3 *Determination of maximum wavelength*

0.5 ml of the parent solution of 400 ppm quercetin and put in a vial, after which it was let to react for 6 minutes with 2 mL of aquadest and 0.15 mL of 5% NaNO₂. Add up to 0.15 mL of 10% AlCl₃ to the solution, and then allow to stand for an additional 6 minutes. After reacting with 2 mL of NaOH 4%, the solution is diluted with aquadest to a final volume of 5 mL and allowed to stand for 15 minutes. highest uptake was seen between 380 and 560 nm in wavelength.

2.2.3.4 *Construction of a calibration curve*

2 mL of aquadest and 0.15 NaNO₂ 5% are added to a total of 0.5 mL of each solution concentration, which is then hushed for 6 minutes. AlCl₃ 10% up to 0.15 mL may be added to the solution; after 6 minutes, let stand once more. Aquadest is used to dilute the 2 mL NaOH 4% solution to a final volume of 5 mL, which is then allowed to stand for 15 minutes. maximal uptake at various wavelengths measured.

2.2.3.5 *Manufacture of blanko solution*

A total of 1 ml of ethanol 96% is reacted with 4 mL aquadest and 0.30 mL NaNO₂ 5% then left for 6 minutes. Add up to 0.30 mL of 10% AlCl₃ to the solution, and then allow to stand for an additional 6 minutes. The solution is diluted with 4 mL of 4% NaOH, followed by 5 mL of aquadest, and allowed to stand for 15 minutes. then determined the greatest absorption between 380 and 560 nm.

2.2.3.6 *Manufacture of extract sample solution*

50 milligrams of the extract were measured and dissolved in 100 mL of 96% ethanol to a mark (500 ppm). After that, the 500-ppm solution is replicated three times. Each replication is given 0.5 mL of the reaction, 2 mL of aquadest, and 0.15 mL of the 5% NaNO₂ after which it is quiet for 6 minutes. The solution is given a final addition of 0.15 mL of AlCl₃ 10% before standing once again for 6 minutes. Aquadest is used to dilute the 2 mL of NaOH 4%-reacted solution to 5 mL, and the mixture is allowed to stand for 15 minutes. highest uptake was seen between 380 and 560 nm in wavelength.

3 RESULTS AND DISCUSSION

To determine the maximum uptake in reading the sample, the maximum wavelength is determined. Maximum delombang length was achieved by 415, and Figure 1 shows the maximum wavelength data.

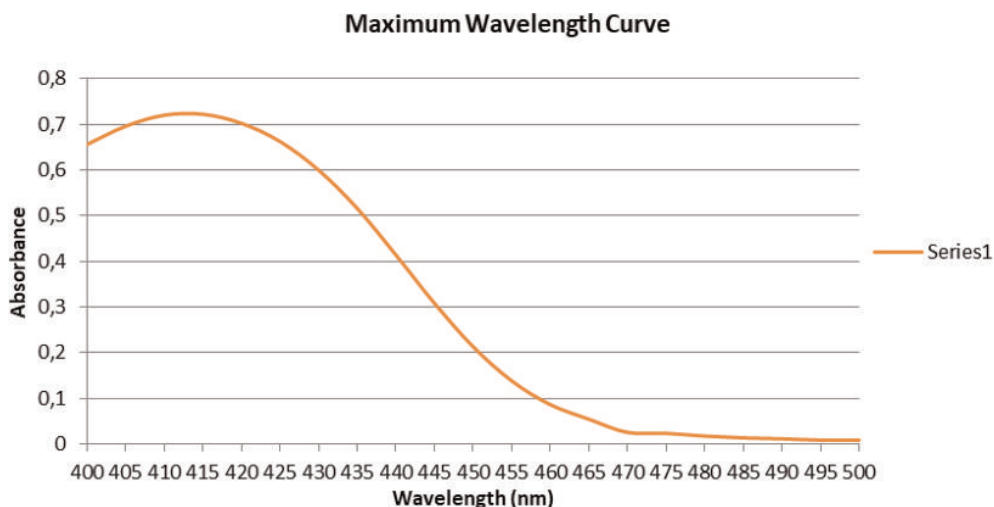


Figure 1. Maximum wavelength.

Table 1. Flavonoid levels of cabbage ceciwis.

Replication	Maceration (%)	Maceration + MAE (%)
1	1.0580	2.0725
2	1.1605	2.2654
3	1.0950	2.1800
Average	1.1045	2.1726

The results of research analysis of flavonoids ceciwis cabbage (*Brassica oleracea* var. *capitata alba*) qualitatively obtained positive results that showed that cabbage ceciwis has flavonoid compounds. Analyses are conducted quantitatively, as shown in Table 1.

According to the information in Table 1, the maceration extraction method with the initial MAE treatment has a higher average total flavonoid content than the direct maceration approach, which has a value of 1.1045%. This difference in outcomes is due to the initial treatment of MAE. This treatment causes the pores in the sample to open and the solvent easily attracts compounds present in the sample.

4 CONCLUSION

The maximum wavelength obtained is 415. Total withdrawal of flavonoid compounds with initial MAE treatment was obtained a value of 2.1726% and without initial treatment of 1.1045%.

ACKNOWLEDGMENT

This research was financed by the Funds of Politeknik Harapan Bersama through the P3M Unit.

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Antioxidant activity test antiaging serum from *Centella asiatica* extract and rose oil

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ABSTRACT: *Centella asiatica* is one of the plants in the form of herbs that have been widely used as medicine. This plant contains secondary metabolites in the form of phenol. The result of other natural ingredients that contain phenol is rose oil. One of the uses of this phenolic compound is as an antioxidant, which is a compound that can counteract free radicals. Antioxidants can affect metabolism in the body, one of which is to prevent aging of the skin. The purpose of this research is to make an antiaging serum that will be tested for its physical properties and antioxidant activity. This research is an experimental research, the data collection method uses qualitative and quantitative data from laboratory experiments. The extract was made by maceration method using 96% ethanol solvent and antioxidant activity test using DPPH reduction with a UV-Vis spectrophotometer instrument. From the results of the preparations made, physical tests were carried out on organoleptic, homogeneity, pH, and adhesion tests and also tested for preference and irritation. The results of the physical test showed that the serum preparation met the provisional requirements for the antioxidant power test, the IC_{50} result was 98,72 ppm so the serum produced had a strong antioxidant power.

1 INTRODUCTION

Currently, many excavations and modifications of natural compounds have been carried out derived from plants in an effort to find new drugs that are safe and selective (Aulia 2016). One of the plants that is useful in medicine is *Centella asiatica* (Artanti & Maryani 2014). The secondary metabolic product of other plants that is widely used is rose oil which is obtained from the distillation of red roses.

Centella asiatica is one of the medicinal plants owned by Indonesia which has been used traditionally for skin diseases, stomachaches, coughs, dysentery, inflammation, and antioxidants. The important and distinctive chemical constituents of *Centella asiatica* are triterpene ester glycoside compounds, namely asiaticoside and madecoside, triterpene group compounds, and phenolic group compounds (Artanti & Maryani 2014). This chemical content can be obtained in the form of extract by maceration method using 96% solvent. Rose oil contains phenolic compounds as well as other compounds such as geraniol, nerol, and citronellal which can function as anti-aging (Fadhilah Karimah 2019).

The phenolic compounds contained in *Centella asiatica* and rose oil function as natural antioxidants. Phenolic compounds have one (phenol) or more (polyphenol) phenol ring, that is the -hydroxy group bonded to an aromatic ring so that it is easily oxidized by donating a hydrogen atom on free radicals. His ability to shape stable phenoxy radicals in oxidation reactions. This causes phenolic compounds to be very potent as antioxidants. Natural phenolic compounds are generally in the form of polyphenols that form ether, ester, or compounds glycosides, including flavonoids, tannins, tocopherols, coumarins, lignins, cinnamic

acid derivatives, and –acids polyfunctional organic (Winarsi 2007). Judging from the function of the compounds it contains, namely as antioxidants, *Centella asiatica* can be used as an antiaging. This is because natural antioxidants from plants can protect the skin from sunlight due to Reactive Oxygen Species and free radicals (Winarsi 2007).

Antioxidants have one benefit, namely as an antidote to the symptoms of antiaging. This symptom is characterized by a decrease in skin moisture and elasticity because the skin's elasticity and ability to hold water has decreased. As a result, the face looks wrinkled, dry, and rough skin, and shows black spots, where this condition is very easily experienced by women, especially those aged 40 years and over (Putri 2017). To facilitate the use of *Centella asiatica* extract and rose oil as antiaging, it is necessary to make a preparation. The dosage form chosen was serum and physical properties were tested on the preparations made. Serum preparations were chosen because they are easier to apply and another reason is that nowadays consumer demand for anti-aging serums is increasing, this is also very likely due to the hot weather in Indonesia which can cause skin damage, especially the face due to direct sun exposure.

To prove the antioxidant activity of the prepared serum, the test in this research was carried out by measuring the caught synthetic radicals in polar organic solvents such as methanol at room temperature. The synthetic radical used is DPPH (2,2-diphenyl-1-picrylhydrazyl). In this method, phenolic compounds as antioxidants will react with free radicals DPPH through the atomic donation mechanism hydrogen and cause DPPH color decay from purple turn yellow (Elfasyari *et al.* 2019).

2 METHODS

Serum preparations are made in the form of a gel with the active ingredients of *Centella asiatica* extract and rose oil. Antioxidant activity test using DPPH attenuation method with UV-Vis spectrophotometer.

2.1 Research tools

The tools used are as follows: Analytical balance, beaker glass, black jar for maceration, stirring rod, flannel, glass funnel, steam dish, test tube, measuring flask, volume pipette, blender, rotavapor, vial, measuring cup, micropipette, cuvette, UV-Vis spectrophotometer (Ganesys 10 S).

2.2 Research material

The materials used were *Centella asiatica* herb, aquadest, chitosan, Tween 80, HPMC, acetic acid, Aethanolum 96%, Methanol, DPPH, and FeCl₃ 5%.

2.3 Research procedure

2.3.1 Making simplicia powder

Cleaned and dry *Centella asiatica* herbs was mashed and sieved with a mess size of 60 to obtain a fine simplicia powder. The simplicia powder obtained was stored in a clean, dry, and tightly closed container.

2.3.2 Phytochemical screening of phenol compounds

The simplicia powder was weighed as much as 2 g, added with distilled water, and heated for about 10 minutes. The results obtained were filtered to separate the extract and the dregs. Then as much as 2 ml of the sample in a test tube was added 5 drops of FeCl₃ to produce a blue or green-black color (Harborne 1987).

2.3.3 *Production of Centella asiatica herb ethanol extract*

Centella asiatica herb *simplicia* powder of as much as 150 g was extracted with 750 ml of 96% ethanol solvent, soaked for 5 days while stirring occasionally, then filtered. The filtrate was evaporated to obtain a thick extract, then a solvent-free test was carried out. The viscous extract obtained was weighed and stored in a tightly closed container (Rompas *et al.* 2012).

2.3.4 *Serum making*

The preparation was made by weighing the HPMC then developed in distilled water, stirred homogeneously to produce a gel base, and then allowed to stand for a while so that the foam disappeared. Chitosan was dissolved in 0.5% acetic acid solution and then mixed with the extract and rose oil that had previously been dissolved in tween 80. Mix until homogeneous.

2.3.5 *Serum preparation test*

2.3.5.1 *Organoleptic test*

Testing was done by visual observation of the serum.

2.3.5.2 *pH test*

Testing was done by pH using a pH meter or pH stick and comparing with the pH literature.

2.3.5.3 *Homogeneity test*

Testing was done on the homogeneity of the serum.

2.3.5.4 *Adhesion measurement*

This test is carried out by spraying the preparation on the arm at a distance of 3 cm. After that, it is counted for 10 seconds to see if the preparation sticks or droplets from the spray drip down.

2.3.5.5 *Irritation test*

It was performed in 10 panelists. The open patch test was carried out by applying the preparation made at the location of the attachment with a certain area (2.5 × 2.5 cm), leaving it open, and observing what happened. This test was carried out once a day for three consecutive days. A positive irritation reaction is indicated by the presence of redness, itching, or swelling on the skin of the treated forearm. The presence of red skin is marked (+), itching (+ +), swelling (+ + +), and those that do not show any reaction are marked (-).

2.3.5.6 *Like test*

The test is to determine the respondent's level of preference for the results of serum preparations.

2.3.5.7 *Analysis of antioxidants in serum preparations*

Prepare: Methanol as a blank solution, DPPH solution with a concentration of 40 ppm, serum sample, and control series solution (Vitamin C). Then the sample and control were read for absorbance at a wavelength of 515 nm.

2.3.5.8 *Antioxidant activity data analysis*

Determination of antioxidant activity using the DPPH method is expressed by the DPPH attenuation value (IC₅₀), the greater the attenuation value, the greater the antioxidant activity value. The percentage of DPPH inhibitory activity in serum is expressed by the formula:

$$\% \text{ inhibition} = \frac{\text{control absorbance} - \text{sample absorbance}}{\text{control absorbance}} \times 100\% \quad (1)$$

The percentage of inhibition data was then graphed between the concentration (x) and % inhibition (y) in order to obtain a linear regression equation $y = ax + b$. By entering the value

of $y = 50$, the IC_{50} value will be obtained. IC_{50} is the concentration required to reduce DPPH by 50%. Then IC_{50} was calculated using a linear regression equation, the sample concentration as the x-axis and % inhibition as the y-axis. From the equation $y = a + bx$, the IC_{50} value can be calculated using the formula:

$$y = ax + b$$

$$50 = ax + b$$

$$(x) IC_{50} = \frac{50 - b}{a}$$

3 RESULTS AND DISCUSSION

This study aims to determine the physical properties and antioxidant power of *Centella asiatica* extract serum and rose oil.

The phenolic compounds in *Centella asiatica* are withdrawn by maceration using 96% ethanol as solvent. Maceration was carried out for 5 days with the aim that the active substance in the simplicia was completely dissolved into the solvent, the principle used in the extraction was an equilibrium reaction between the active substance and the solvent. During the immersion process, the cell walls and cell membranes will break down due to the pressure difference between the outside of the cell and the inside of the cell so that the secondary metabolites in the cell will be dissolved in the organic solvent used (Chairunnisa *et al.* 2019). Meanwhile, rose oil is obtained directly from the laboratory. To determine the content of the active substance, namely phenolic compounds, a qualitative test was carried out. The test results obtained a blackish-green color after the simplicia was added with $FeCl_3$ reagent, this indicates that the tested sample contains phenolic compounds (Lotulung *et al.* 2015).

The serum preparations that have been made are then evaluated for preparations to determine whether the serum made is in accordance with the standard when viewed from the physical tests and irritation tests that have been carried out. The results of the physical tests carried out are as follows:

Table 1. Table of physical test results for serum preparations.

No	Test Criteria	Test Results		
		Replication 1	Replication 2	Replication 3
1	Organoleptic test			
	Shape	Thick		
	Color	Greenish Yellow		
	Smell	Rose oil smell		
2	Homogeneity test	Homogeneous		
3	pH test	5	5	5
4	Adhesive test	2 second	3 second	2 second
5	Irritation test	No irritation		

3.1 Organoleptic test

Organoleptic observations of the preparations showed that the gel preparations produced were greenish-yellow in color and viscous. The aroma that is generated is the distinctive smell of rose oil.

3.2 *Homogeneity test*

The results of the homogeneity of spray gel preparations that have been made are homogeneous because there are no coarse grains, this can be seen from the visual test carried out by dripping a small amount of the gel preparation onto the surface of the glass slide, and then covering it with another glass preparation.

3.3 *pH test*

The pH test aims to evaluate the pH of serum preparations so that they are suitable. The pH test was carried out three times as shown in Table 1. The pH value of the preparation has met the requirements, which is in the range of 4.5–6.5 (Winarsi 2007), thus the serum preparation made is safe to be applied to the skin.

3.4 *Adhesion test*

The serum adhesiveness is used to calculate how long it takes the serum to spread and adhere to the skin surface. The results of the adhesive dispersion test were obtained in 3 replications at 10 seconds dripping down or not sticking. The resulting drip speed result is less than 10 seconds (Winarsi, 2007).

3.5 *Irritation test*

Irritation test is carried out on serum preparations made to know whether the preparations can cause irritation to the skin or not. Irritation can be divided into two categories, namely primary irritation, which will appear immediately after the attachment or contact with the skin, and secondary irritation, which occurs only a few hours after touching or sticking to the skin.

Based on the results of the irritation test on 10 respondents by applying the preparation made on the forearm to all respondents, all respondents gave negative results or there were no signs indicating an irritation or allergic reaction such as redness, itching, and swelling of the preparations made.

3.6 *Like test*

This test was carried out to know whether the serum formula made was preferred by the respondents. Assessment of the preparation was carried out by giving a questionnaire based on several characteristics possessed by the preparation, namely aroma/smell, color, and convenience of using spray gel preparations with the highest value parameters being likes, dislikes, and dislikes. This test was followed by 10 respondents who were chosen randomly. The results showed that respondents chose like = 5, disliked = 3, and did not like = 2.

The results of the preference test show that of the 10 respondents who tried this serum gel preparation, they chose less like and dislike based on the color of the gel preparation. because the panelists said that the color of the preparation produced was less attractive. Meanwhile, for respondents who chose to like it based on the taste on the skin and the fragrant smell of rose oil produced reported feeling a cold sensation when applied to the skin.

3.7 *Antioxidant activity test with DPPH method*

Antioxidant activity examination by spectrophotometry was carried out by reacting serum samples with free radical DPPH solution. The absorbance measurement data at 515 nm is shown in the following figure:

Table 2. Antioxidant test results.

Concentration	Concentration log	Probit
50	1,69	4,42
100	2,00	4,67
200	2,30	5,03
400	2,60	5,47

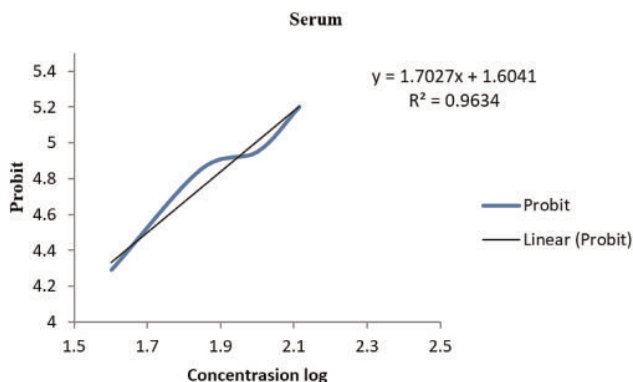


Figure 1. Serum linear regression results.

From Figure 1, the value of $y = 1,7027x + 1,6041$ is obtained with a value of $r = 0,9634$. Results of the test show that the solution DPPH added test produces absorbance count, which means serum preparations are able to reduce DPPH which are free radicals. From the result, absorbance obtained later calculated the percent inhibition of DPPH, which shows the magnitude of the activity antioxidant serum test solution against free radicals (DPPH) (Elfasyari *et al.* 2019).

The smaller the required sample concentration to reduce serum by 50%, the activity of antioxidants are said to be stronger. The absorption value of the DPPH solution to the sample was calculated as percent inhibition (% inhibition). Based on the results of the calculation of antioxidant activity obtained results that the IC_{50} value is 98,72 $\mu\text{g/mL}$. Specifically, a compound is said to be a very strong antioxidant if the IC_{50} value is less than 50 ppm, strong for IC_{50} is 50–100 ppm, moderate if it is 100–150 ppm, and weak if the IC_{50} value is 151–200 ppm (Bahriul *et al.* 2014). From the results, it was found that the serum had strong antioxidant power.

From the overall results, of the physical test on the preparation, the serum made has met the required standards. This can be seen from the results of the organoleptic test, homogeneity, pH, adhesion, liking, and irritation test. The serum is made with the active ingredients of *Centella asiatica* extract and rose oil as well as additional ingredients of HPMC, chitosan, aquadest, 0.5% acetic acid, and Tween 80. The choice of HPMC as the gelling agent is because Hydroxy propyl methyl cellulose (HPMC) is a semi-synthetic gelling agent derived from cellulose which is resistant to phenol and stable at pH 3–11. HPMC can form a clear gel and is neutral and stable in long-term storage. Chitosan is used because it is not toxic, is a good coagulant, and easily forms membranes and gels, making it suitable for use in cosmetic preparations. Acetic acid is used as a solvent for chitosan, this is because chitosan is a substance that quickly dissolves in organic acids, one of which is acetic acid. The use of Tween 80 in preparations as a wetting agent, as well as an emulsifier and solubility enhancer, also functions as a penetration enhancer (Putri 2017).

Meanwhile, for the antioxidant activity test, it was found that the serum made had strong antioxidant power. The phenolic compounds in *Centella asiatica* extract and rose oil can function as natural antioxidants in the serum preparation. The antioxidant activity of phenolic compounds is directly related to the chemical structure such as the degree of glycosylation and the number and position of the hydroxyl groups associated with the carboxyl functional groups. These compounds make an important contribution to antioxidant activity because they have activity in scavenging free radicals. Free radicals have harmful effects on biological systems. Phenolic compounds have the ability to donate hydrogen atoms or electrons to free radicals to form stable intermediates. These compounds bind to free radicals and decompose oxidation products (Diniyah & Lee 2020). It is possible that the combination of phenolic compounds from the two active ingredients in the serum, namely *Centella asiatica* and rose oil, work synergistically as natural antioxidants to produce a serum with strong antioxidant activity. This is in line with previous studies that the combination of phenolic compounds from two types of plants will produce a stronger IC50 value than in its single form (Taswin & Nurjanah 2021). This result is an expectation that the serum can be used as an antiaging in cosmetic preparations, especially for the needs of facial skin.

4 CONCLUSION

From the results obtained, the serum *Centella asiatica* extract and rose oil have met the requirements of the physical test and have a strong antioxidant power.

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Basal Energy Requirements (BER), visceral fat, and cell age on Body Mass Index (BMI) in teenagers

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ABSTRACT: Adolescent nutritional status can be calculated based on Body Mass Index (BMI). Data Riskesdas 2018 shows that 25.7% of adolescents aged 13–15 years and 26.9% of adolescents aged 16–18 years with short and very short nutritional status. In addition, there are 8.7% of adolescents aged 13–15 years and 8.1% of adolescents aged 16–18 years with thin and very thin conditions. Poor food consumption in adolescents can cause an imbalance between energy intake and output which can lead to stunting. This study aims to determine the description of BMI and its relationship with Basal Energy Requirements (BER), Visceral fat, and Cell Age in the adolescent group using the Bioimpedency Analysis (BIA) tool. Quantitative research method with a cross-sectional approach with a sample of early teens RT 02 RW 01 Kudaile Village with a total of 44 respondents taken by Accidental Sampling. The results of the study based on BMI were 59.09% in the normal category while 22.73% were overweight and 18.18% were underweight, the average BER of the respondents was 1197.64 kcal and 70.45% had normal visceral fat. About 29.55% had abnormal abdominal fat, 79.55% had younger cell ages, and 20.45% had cells older than their chronological age. Underweight adolescents with cell age older than their chronological age can be detected to implement changes in behavior and healthy lifestyles.

1 INTRODUCTION

Nutritional problems are related to a person's health problems. An imbalance of intake with body needs can result in less or more nutrition. Technological developments in the fields of technology and education make it easier for humans in general to bring changes, especially the behavior of consuming instant food to save time in everyday life. A person is definitely more likely to like a fast activity than a long one (World Health Organization 2018).

The phase of rapid growth and development is owned by adolescents and this period also requires large amounts of nutrition to balance daily calorie needs. Consumption of food that is not appropriate with low calories makes the body become unbalanced, resulting in a lack of nutrition for adolescents so that growth and development become stunted (*stunting*) (Yang *et al.* 2020). Nutritional status in adolescents is calculated by Body Mass Index (BMI). Based on basic health research data Riskesdas, 2018, 25.7% of adolescents aged 13–15 years and 26.9% of adolescents aged 16–18 years reported short and very short nutritional status. In addition, there are 8.7% of adolescents aged 13–15 years and 8.1% of adolescents aged 16–18 years with thin and very thin conditions (Bentham *et al.* 2017). In the province of Central Java, the prevalence of undernutrition reached 9.9% and overnutrition was above the national prevalence of 2.8%. Another nutritional problem in school-age

children, especially teenagers, is the low consumption of energy and protein below the minimum requirement, namely 44.4% and 30.6%.

Makarimah (2018) research on the relationship between body weight, body fat, nutritional status, maternal age at menarche, and age at menarche in students at SDN Cikaret 01 Cibinong Bogor found a relationship between percent body fat, nutritional status, and age of menarche.

Meanwhile, according to Auliyah's research in 2012, that there was a relationship between BMI, body fat, and physical activity with central obesity (Auliyah 2012).

According to Peng Ju Liu, the adjusted odds ratios (95% CI) for the presence of MetS in the highest FMI quartile versus the lowest quartile were 79.143 (21.243–294.852) for men ($P < 0.01$) and 52.039 (4.144–653.436) for women ($P < 0.01$) after adjusting age, BMI, BF%, TC, LDL, CRP, smoking status and exercise status, and the odds ratios were 9.166 (2.157–38.952) for men ($P < 0.01$) and 25.574 (1.945–336.228) for women ($P < 0.05$) when WC was also added into the adjustment. It was determined that BMI values of 27.45 and 23.85 kg/m², BF% of 23.95% and 31.35%, and FMI of 7.00 and 7.90 kg/m² were the optimal cutoff values to predict the presence of MetS among men and women according to the ROC curve analysis. Among the indicators used to predict MetS, FMI was the index that showed the greatest area under the ROC curve in both sexes (Reaven 2008).

Akseer research Adolescence and emerging adulthood form a critical time period for the achievement of optimal health and nutrition across all stages of the life course. We reviewed published literature and global data repositories for information on nutrition levels, trends, and patterns among young people aged 10–24 years from January 1, 2016 to September 20, 2016. The results of this study showed a less-than-ideal picture of current young people's nutrition, suggesting dual burdens of underweight and high body-mass index in many countries and variable improvements in micronutrient deficiencies across geographical regions. Poor diet diversity and lack of nutrient-dense food, high risk for metabolic syndrome, and sedentary lifestyles also characterize this population (Akseer *et al.* 2017). This study aims to determine the description of BMI and its relationship to Basal Energy Requirements (BER), Visceral Fat, and Cell Age in the adolescent group using the Bioimpedency Analysis (BIA) tool.

2 METHODS

The research design uses a quantitative descriptive approach, using a cross-sectional design where measurements of BMI will be carried out *Basal Energy Requirements (BER)*, abdominal fat, and cell age at the same time. The sample of early teens RT 02 RW 01 Kudaile Village with a total of 44 respondents was taken by accidental sampling. Data analysis was carried out using *Chi-Square and T-test* so that they could determine the relationship between BMI and BER, BMI with abdominal fat, and BMI with cell age.

3 RESULTS AND DISCUSSION

Table 1 states that the distribution of respondents based on the largest BMI is 26 (59.09%) with normal BMI (18.5–25), 10 (22.73%) with obesity, and 8 (18.18%) with thin respondents.

Table 1. Distribution of respondents based on BMI.

IMT	The number of	Percentage
≤ 18.4	8	18.8
18.5–25	26	59.09
≥ 25.1	10	22.73
Total	44	100

BMI is a measure of nutritional status from the ratio of weight and height. The BMI of respondents is categorized according to the Indonesian Ministry of Health, namely thin (<18.4), normal (18.5–25), and obese (>25).

Based on Table 2, it is stated that the distribution of respondents based on the largest BMI is 26 (59.09%) with a normal BMI (18.5–25), 10 (22.73%) with an obese BMI, and 8 (18.18%) with thin. This is in line with the results of the study by Suryana (2017) regarding the Relationship of Physical Activity with BMI and Body Composition, which showed that 64.6% of respondents had a normal BMI, 13.8% were underweight, and 13.8% were obese.

Table 2. Distribution of respondents based on Basal Energy Requirements (BER).

Variables	Mean	SD	Min-Max	95% CI
BER	1374	242,144	1078–2047	1316.16–1455.18

Table 2 states that the average BER of the respondents is 1374 Kcal (95% CI 1316.16–1455.18) with a Standard Deviation of 242.144.

Table 3. Distribution of respondents based on visceral fat.

Visceral Fat	The Number of	Percentages
≤ 3	31	70.45
> 3	13	29.55
Total	44	100

Table 3 states that the distribution of respondents based on the percentage of visceral fat is 31 respondents (70.45%) have a percentage of visceral fat less than equal to 3, while 13 respondents (29.55%) have a percentage of visceral fat more than 3.

Table 4. Distribution of respondents by cell age.

Cell Age	The Number of	Percentages
≤ age	35	79.55
> age	9	20.45
Total	44	100

Table 4 states that the distribution of respondents based on cell age is 33 respondents (78.6%) who have a cell age younger than or equal to chronological age, while 9 respondents (21.4%) have a cell age older than their chronological age.

Table 5. Distribution of respondents based on BMI and BER.

IMT	Mean	SD	SE	P Value	N
Normal	1339.42	183.376	37.926	0.216	26
abnormal	1431.29	270.462	70.110		16

Table 5 states that the average BMR with a normal BMI is 1349.42 with a standard deviation of 193.386, while the average BMR with an abnormal BMI is 1441.19 with a standard deviation of 280.442. Having a p-value of 0.216 at 5% alpha means that there is no significant difference in the average BMR between respondents with normal and abnormal BMI.

Table 6. Distribution of respondents based on BMI and visceral fat.

Visceral fat	IMT						P value
	Normal		abnormal		Total		
	n	%	N	%	n	%	
≤ 3 (normal)	23	74.2	8	25.8	31	100	0.126
> 3 (abnormal)	5	38.5	8	61.5	13	100	
total	28	63.6	16	36,4	44	100	

BER is the minimum energy requirement to carry out vital body processes. Factors that can affect BER are gender, age, body size, body composition, health level, body temperature, activity, nutritional status, smoking habits, and pregnancy and breastfeeding. Based on the results of the study, it was stated that the average BER of the respondents was 1374 Kcal (95% CI 1316.16–1455.18) BER with a normal BMI was 1339.4 with a standard deviation of 183,376 while BER with an abnormal BMI was 1431.29 with a standard deviation of 270,462. With a p-value of 0.216 at 5% alpha, it means that there is no significant difference in the average BER between respondents with normal and abnormal BMI.

The theory states that BER is influenced by gender, age, body size, health level, body temperature, activity, hormone secretion, nutritional status, smoking, and pregnancy and breastfeeding. So by knowing BMI and BER a person can control their weight. BER can also be used to determine the calories needed/day (Sajith 2018).

Table 6 states that the distribution of respondents based on visceral fat with BMI obtained that there are as many as 23 (74.2%) respondents with visceral fat less than 3 have normal BMI, while 5 (38.5%) respondents have visceral fat more than 3 have normal BMI. At a P value of 0.126, it can be concluded that there is no difference between normal and abnormal BMI for abdominal fat (Ferretti *et al.* 2015).

The human body has a composition of fat and non-fat (Okeyo *et al.* 2019). Fat is widely distributed more than 50% in the subcutaneous tissue, the other in the abdominal cavity by 45% which is called abdominal fat, and 5% in the intramuscular tissue (Woday *et al.* 2018). The visceral fat is fat in the abdominal area.

According to the theory, visceral fat affects body weight. BMI is an indicator of nutritional status from the calculation of height and weight, so visceral fat is a component of the body that can affect BMI. The results of this study indicate that there is no relationship between BMI and abdominal fat values and the cause is due to the limitations of the study sample (Ramírez-Vélez *et al.* 2017).

Table 7. Distribution of respondents based on BMI and cell age.

Cell Age	IMT						OR 95% CI	P value
	Normal		Tidak		Total			
	n	%	N	%	n	%		
≤ chronological age	28	80	7	20	35	100	1.435	0.00
> chronological age	3	33.3	6	66,7	9	100		
Total	31	70.5	13	29.5	44	100		

Table 7 states that the distribution of respondents based on cell age with BMI obtained that there are as many as 28 (80%) respondents with cell age younger or equal to their chronological age have normal BMI and 3 (33.3%) respondents have cell age is older than chronological age with normal BMI. At a P value of 0.00, it can be concluded that there is a difference between normal BMI and abnormal BMI with respect to the age of the respondent's cells.

Age represents the age of body cells that describe how old a person looks. Cell age can be different from its chronological age (age date of birth). The causes include stress, chemicals, lack of rest, and unhealthy lifestyle.

The results showed that the distribution of respondents based on cell age with BMI obtained that 28 (80%) respondents with cell age younger or equal to their chronological age had normal BMI and 3 (33.3%) respondents had cell age older than chronological age with normal BMI. A p-value of 0.00 indicated a difference between normal BMI and abnormal BMI with respect to the respondent's cell age (Gomez-Arbelaez *et al.* 2017).

This is in line with the research of Djuartina, Tena *et al.* about the factors that cause differences in biological age and chronological age in the elderly, there is a strong relationship between biological age and BMI ($p = 0.012$) (Chi *et al.* 2017).

In this study, it was found that 79.5% of respondents had a cell age younger than or equal to their chronological age. This can be because this research was conducted on adolescents aged 11–16 years at a very young age. Only adolescents with abnormal visceral fat had a cell age older than their chronological age (Vandewater *et al.* 2015). The limitation of this study is the number of respondents, which is only 44 people; of course, it is still not enough to describe the actual situation and more variables need to be added.

4 CONCLUSION

There was no significant difference between BMI, BER, and visceral fat, but there was a significant difference between BMI and cell age in the adolescent group.

Recommendations based on the results of the study found that BMI, BER, and abdominal fat in adolescents who are overweight and obese or have cell age older than their chronological age can be used as behavior modification and healthy lifestyles as a screening for adolescents who are overweight, obese and older cell age. older than the chronology. For future researchers to be able to do more research about variables related to BMI in adolescents who have not been studied in this study such as body image, physical activity, breakfast habits, and nutrient intake.

ACKNOWLEDGMENTS

The authors thanks Harapan Bersama Polytechnic for supporting this research. Gratitude was also conveyed to respondents in the Tegal Regency who are willing to be respondents in this study.

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Correlation between the epidemiological investigation activities and larva free index on the incidence rate of dengue haemorrhagic fever

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ABSTRACT: Several COVID-19 cases encountered at the beginning of 2020 were initially diagnosed as cases of DHF. For this reason, it is necessary to monitor the number of DHF cases and the factors that influence the risk of developing dengue so that the DHF cases can be suppressed. Several efforts to control DHF include carrying out epidemiological investigation activity and monitoring the number of *Aedes Aegypti* DHF mosquitoes through the larva-free index indicator. The purpose of this study was to analyze the correlation between epidemiological investigation activity and the larva-free index on the Incidence Rate (IR) of DHF in Tegal City in 2020. This research was a quantitative analytic study with a cross-sectional design. The population in this study was DHF patients in Tegal City, with sub-districts as the unit analysis about 27 sub-districts. The analysis was carried out with the Pearson product-moment correlation test. The results show a correlation between epidemiological activities and the number of IR DHF (p-value: 0.033; r: 0.411). There was a correlation between the larva-free index and IR DHF (p-value: 0.043; r: 0.392). Therefore, it is necessary to increase the percentage of epidemiological investigation activity and the larva-free index in each sub-districts to reduce the risk of DHF in the sub-district.

1 INTRODUCTION

Dengue Hemorrhagic Fever (DHF) is an endemic disease in the tropics and subtropics, including Indonesia. In 2018 the number of DHF sufferers in Indonesia was 16,441 people spread over 440 regencies and increased to 40,525 in 2019, spread over 481 out of 514 regencies in Indonesia. Until March 2019, the number of deaths due to DHF also increased from 118 people in 2018 to 354 people in 2019. In 2019, the incidence of DHF in Indonesia increased to 51.48% compared to 2018, which was 24.75% (Maharsi *et al.* 2020). Until May 2020, Central Java was in eighth place with the most DHF cases in Indonesia, with 2,176 DHF cases out of 52,929 DHF cases in Indonesia. Deaths due to DHF in Central Java also ranked 2nd, with 38 deaths out of 328 cases of DHF deaths in Indonesia (Tarmizi 2020).

The need for controlling DHF cases, including during the COVID-19 pandemic, is stated in the Circular Letter of the Ministry of Health number HK.02.02/IV/2360/2020 about the Implementation of Prevention and Control of Dengue Hemorrhagic Fever in a COVID-19 Pandemic Situation. It stated a cross-reaction with flaviviruses and non-specific viruses (including COVID-19). So for patients with a positive dengue IgM serologic examination (Direktorat Jenderal Pencegahan dan Pengendalian Penyakit (P2P) 2020). Several cases of COVID-19, in the beginning, were found with a diagnosis of dengue fever (Kosasih 2020). It is necessary to monitor the number of dengue cases, among others, through dengue surveillance activities (Tarmizi 2020).

DHF surveillance itself is the process of collecting, processing, analyzing, and interpreting data, as well as disseminating information to program organizers, agencies, and related

parties systematically and continuously about the DHF situation and conditions that affect the increase and transmission of the disease so that action can be taken control efficiently and effectively (Hariro *et al.* 2019). One of the aims of implementing DHF Surveillance is to monitor the trend of DHF disease and follow-up on DHF case reports by carrying out Epidemiological Investigation activities and taking necessary countermeasures (Arista *et al.* 2021).

Epidemiological investigations in dengue cases are carried out by tracking other sufferers/suspects and checking for mosquito larvae that transmit DHF in the patient's/suspect's house and surrounding houses within a radius of at least 100 meters, as well as public places that are estimated to be a source of further spread of the disease. If the Epidemiological Investigation activities results are positive (found one or more other DHF sufferers and three suspected DHF, and larvae are found ($\geq 5\%$), then focused countermeasures are carried out (fogging, counseling, mosquito nets eradication, and selective larvacidation) because if negative is carried out Counseling, Eradication of Mosquito Nests and selective larvacidation. By implementing The Epidemiological Investigation activities, the occurrence of dengue transmission can be known/identified early so that it does not spread to a wider area so that the greater the Epidemiological Investigation Activities value in a place, the smaller the risk of transmission of dengue fever in that place (Kementerian Kesehatan RI 2017).

Dengue fever is an infection caused by the dengue virus, which spreads from person to person through the bite of the *Aedes aegypti* (Ae. Aegypti) (Yuniyanti *et al.* 2021). Therefore, the vector density of *Aedes Aegypti* also needs to be monitored through periodic flick checks. Periodic larva inspection is carried out regularly every week or at least once in 3 months by each Public Health Center in every village. The examination was carried out on 100 samples of houses/buildings, which were chosen randomly to know the Larva free index. The higher the value of the Larva free index in a place, it is hoped that the risk of transmission will be more negligible in that area. Epidemiological measures that are often used in dengue control activities are Incidence Rate (IR), Case Fatality Rate (CFR), Attack Rate (AR). IR is a measure that shows the speed of occurrence/cases (new) of the disease in the population. The more Incidence indicates the more new cases. With more and more new cases in a place, of course, the risk of transmission in that place is getting more extensive (Kementerian Kesehatan RI 2017).

DHF cases in Tegal city until the end of February 2020 were 12 cases of DHF. While in the previous year, in January 2019, there were 90 cases of DHF. For this reason, it is necessary to know that The DHF control efforts carried out include epidemiological investigation activities and larva-free index in each village so that the spread of DHF cases can be detected early and the number of DHF cases in Tegal city can be suppressed. Several studies on DHF are mostly related to the factors that cause DHF, such as patient characteristics (Hartati *et al.* 2021; Jacqueline Kyungah Lim *et al.* 2021; Kusmintarsih *et al.* 2018; Martini *et al.* 2019; Sulistiawati *et al.* 2020) and behaviors that increase the risk of developing DHF (Baequni *et al.* 2019; Junias & Riwu 2020; Mubarok *et al.* 2018; Palupi *et al.* 2020; Prastiani & Prasasti 2020; Pratiwi *et al.* 2021). In those studies, individuals were used as the unit of analysis. Meanwhile, in this study, the study's object was sub-districts.

This study aimed to analyze the correlation between the Epidemiological Investigations Activities and the larva-free index with the Incidence Rate of DHF in Tegal City and the village as the unit of analysis. The study results can be used to evaluate the success of the DHF eradication program in reducing the risk of DHF transmission.

2 METHODS

This study was a quantitative analytic study with a cross-sectional design. The population in this study were DHF patients, with the unit analysis being the sub-district. The samples in this study were all sub-district in Tegal City, about 27 sub-districts. We used secondary data

from recording dengue cases at the Tegal City Health Office from January to May 2020. The analysis was conducted to decide the correlation between epidemiological investigation activities and the incidence of dengue fever according to urban areas in Tegal City using the Pearson product-moment correlation test. The percentage of Epidemiological Investigations was calculated by multiplying the number of DHF cases followed up by Epidemiological Investigation activities multiplied by the number of DHF cases in each village multiplied by 100%. Meanwhile, the Larva free index was calculated by dividing the number of houses/buildings where the number of houses or buildings did not find larvae inspected multiplied by 100% (Direktur Jendral Pengendalian Penyakit dan Penyehatan Lingkungan 2017).

3 RESULTS AND DISCUSSION

In the health program to eradicate infectious diseases, five categories of interventions need to be considered, namely surveillance, discovery, treatment, prevention, and promotion to overcome the health problem or disease in question. Surveillance is the primary intervention priority because surveillance is helpful to make sure that continuous and quality information is produced so that it can be used as a basis for consideration for making decisions in taking effective and efficient control or countermeasures (ARfan & Taufik 2017).

During the COVID-19 pandemic, the implementation of prevention and monitoring of DHF is carried out through fogging, epidemiological investigations, and dengue diagnosis. It is also conveyed that any positive results from establishing a DHF diagnosis must be followed up with Epidemiological Investigations. Data from epidemiological investigations to show the potential for further transmission and spread of DHF and types of prevention. Epidemiological investigation data related to fogging, abatization, mosquito nets eradication, and counseling data to decide the accuracy of the types of countermeasures with the results of epidemiological investigations (Direktorat Jenderal Pencegahan dan Pengendalian Penyakit (P2P) 2020).

Table 1. The IR of DHF, larva free-index, and epidemiological investigation.

No	Sub-districts	Number of dengue cases	IR	Larva free index	Epidemiological Investigation (%)
1.	Mangkukusuman	0	0	0	0
2.	Mintaragen	2	1.18	1.1	0
3.	Panggung	4	1.33	3.7	25
4.	Slerok	4	2.37	2.56	0
5.	Kejambon	1	0.81	4.5	0
6.	Tegalsari	2	0.83	2.95	100
7.	Kraton	5	3.21	1.23	80
8.	Muarareja	1	1.41	1.5	100
9.	Pekauman	2	2.44	1.75	0
10.	Debong Lor	0	0	0	0
11.	Kemandungan	1	2.6	5.7	100
12.	Pesurungan Kidul	0	0	0	0
13.	Debong Kidul	1	1.8	0.1	100
14.	Bandung	2	3.24	2.7	0
15.	Tunon	3	4.59	2.9	100
16.	Keturen	3	6.09	3.63	67
17.	Kalinyamat Wetan	0	0	0	0
18.	Randugunting	6	3.14	1.73	17
19.	Debong Tengah	2	1.5	4	0
20.	Debong Kulon	2	4.06	0.9	50

(continued)

Table 1. Continued

No	Sub-districts	Number of dengue cases	IR	Larva free index	Epidemiological Investigation (%)
21.	Margadana	8	5.02	3.81	50
22.	Kalinyamat Kulon	1	1.63	5.8	100
23.	Sumur Panggang	2	2.73	5.37	50
24.	Pesurungan Lor	2	3.76	3.6	50
25.	Kaligangsa	2	1.68	3.2	0
26.	Krandon	1	1.37	3.2	0
27.	Cabawan	0	0	0	0
Average			2.58		65.93

Based on Table 1 shows that the highest IR is in Keturen (IR: 6.09), followed by Margadana (IR: 5.02) and Tunon (IR: 4.59). There are only six sub-districts that carry out epidemiological investigations activities 100%, and five sub-districts did not carry out epidemiological investigation activities because there were no cases of DHF there. At the same time, the rest are sub-district that carry out epidemiological investigations activities less than 100% (15 sub-district).

Table 2. Correlation of epidemiological investigation and larva free-index with IR DHF.

		Incidence rate	Hypothesis Conclusion
The Epidemiological Investigation Activities	Pearson correlation	0.411	Medium correlation
	Sig. (2-tailed)	0.033	There is a correlation
	N	27	
The Larva Free Index	Pearson correlation	0.392	Medium correlation
	Sig. (2-tailed)	0.043	There is a correlation
	N	27	

The IR of a disease in a particular place indicates the risk of contracting the disease; the more significant the IR of an area, the greater the risk of transmitting disease. If each case is immediately followed up with epidemiological investigation activities, it can be detected earlier to reduce the number of DHF cases. Table 2 shows a correlation between epidemiological investigation activities and dengue fever incidence rate, which is indicated by the p-value: 0.033 (less than 0.05). The results of this study are in line with Sutriyawan *et al.*, namely the relationship between health service programs and the incidence of DHF with health counseling (0.000), larva examination (0.014), larvicide administration (0.013), and fogging (0.000) (Sutriyawan *et al.* 2022). Based on a systematic review conducted by Angelina and Windraswara, it was stated that epidemiological surveillance is an urgent thing to control the spread of DHF (Angelina & Windraswara 2019).

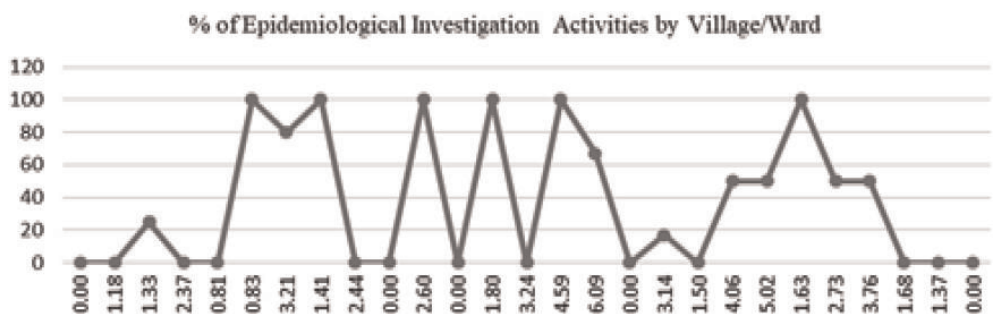


Figure 1. Graph of correlation between epidemiological investigation activities and IR DHF.

Figure 1 shows that most epidemiological investigation activities are still less than 100%. Sub-districts with 100% Epidemiological Investigation activities tend to have lower incidence rates, namely 0.83, 1.41, 2.60, 1.80, and 1.63. Meanwhile, sub-districts with less than 100% of epidemiological investigation activities tend to do higher DHF incidence rates of 4.06, 5.02, 3.76 and even reach 6.09. However, in certain sub-districts, namely Tunon, the incidence rate is higher even though epidemiological investigation activities have been carried out 100%, which is 4.59. Therefore, the relationship between the Epidemiological Investigation activity variable and the incidence rate is moderate ($r : 0.411$). The inconsistency in the level of relationship between the two variables is probably due to the significant incidence of DHF influenced by many factors such as rainfall, population density, air temperature, and air humidity (Angelina & Windraswara 2019).

Periodic larva monitoring produces Flick-free data that describes the spread of mosquitoes in an area. In addition, the Larva free index is also used to decide the endemicity status of a region. While the IR DHF shows probability to be exposed to the disease at a particular time. The study results show a relationship between a Larva free index and Incidence Rate (ρ -value: 0.043; $r : 0.39$).

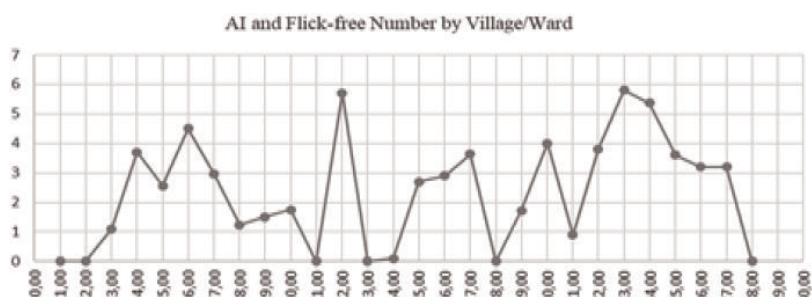


Figure 2. Graph of correlation between the larva free index and IR DHF.

This result is in line with Retno’s study showed a relationship between a Larva free index and IR (Hastuti & Hendrati 2021). However, the level of relationship between a Larva free index and IR is moderate. This is possibly due to other factors that affect IR, such as population mobility and population density factors (Angelina & Windraswara 2019).

The limitation of this study was that data collection was conducted at the beginning of the COVID-19 pandemic, and lockdown regulation was being carried out in Tegal City. So that communication with the Tegal City Health Office is hampered. The Tegal City Office focuses on controlling and handling COVID-19.

4 CONCLUSION

The results of this study show a significant relationship between Epidemiological Investigation activities and IR DHF by the urban village in Tegal City in 2020 with a moderate level of relationship and a positive direction (p -value: 0.033 and $r : 0.411$). There is also a significant relationship between a Larva free index and IR DHF by village with a moderate level of relationship and a positive direction of the relationship (p -value: 0.043 and $r : 0.392$). Implications for further research, it is necessary to carry out further studies that examine the process of carrying out Epidemiological Investigations and Larva-free index activities in each sub-districts.

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Formulation and physical test of guava and lime peel-off mask

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ABSTRACT: Peel-off masks have been developed as a face care cosmetic preparation in liquid form. Guava fruit (*Psidium guajava*) contains flavonoids that are effective in removing acne and clearing blackheads. Lime (*Citrus aurantifolia*) contains flavonoids used as a skin rejuvenator. This study aims to identify the flavonoid compounds contained in guava (*Psidium guajava*) and lime (*Citrus aurantifolia*) and the best concentration as a peel-off mask preparation. The research design made three peel-off mask formulas, each formula carried out three replications, statistical analysis using one-way ANOVA. A comparison of lime and guava in formula I (5%:9%), formula II (7%:7%), and formula III (9%:5%) can be seen, while the additives have the same concentration. Based on the research results, guava and lime contain flavonoid compounds which are indicated by the formation of an orange-red colored solution through the addition of concentrated ethanol, concentrated HCl, and magnesium. The formula I, II, and III have a pH of 5, the density of formula I (1.033 g/ml), formula II (1.031 g/ml), and formula III (1.030 g/ml). The viscosity of formula I (1,723 cP), formula II (1,311 cP), and formula III (1,292 cP) is shown. The homogeneity test on formulas I, II, and III was homogeneous and there was no precipitate. It was concluded that guava and lime contain flavonoid compounds, and the best concentration as a peel-off mask preparation was formula II.

1 INTRODUCTION

Masker Peel-off masks have been developed as a topical application of facial and neck care cosmetics (Yeom *et al.* 2011). Peel-off is applied to form a thin elastic layer (Rahmawanty *et al.* 2015), used for 15–20 minutes even some peel-off masks are used overnight for better results (Budiman *et al.* 2017). The active substances and additives in the mask can penetrate the skin and supply the needed substances in a short time (Kulkarni *et al.* 2019). Peel-off functions to clean, moisturize, shrink pores, and remove dead skin cells deposited in the stratum corneum so that the skin becomes more elastic (Grace *et al.* 2015). Peel-off is useful for removing blackheads, tightening the skin, relaxing facial muscles, preventing wrinkles, and as a refresher (Vieira *et al.* 2009).

Skin is the outermost covering of the human body that protects it from environmental influences. Some indications of aging on the skin include wrinkles, black spots on the face, dry skin, and loss of fat, resulting in the skin losing its smoothness (Melfa *et al.* 2020). All of these symptoms require treatment to slow the loss of natural collagen (Syakri *et al.* 2021). The ability of the skin to repair itself continues to decline and collagen will decrease so that the skin loses its elasticity (Cadet *et al.* 2001). Treatment using antioxidants is a strategy to prevent premature aging. Polyphenol compounds are one of the most antiaging substances because they can prevent oxidation reactions on the skin (Shanbhag *et al.* 2019). Antioxidants are commonly used in skincare products to protect the skin from free radicals (Ginting *et al.* 2020).

Natural sources of plants have been used for centuries in Indonesia to treat various health problems. Currently, one of the plants that are widely cultivated as phytopharmaceutical is

guava (*Psidium guajava*) (Nugraha & Keller 2011). Guava plants (*Psidium guajava*) are widely distributed throughout the world, especially in tropical countries, including Indonesia (Sudira *et al.* 2019). This plant has biological activities including antidiarrheal, antimicrobial, antioxidant, hepatoprotective, antiallergic, antispasmodic, anti-diabetic, anti-inflammatory, and antitussive (Sanda *et al.* 2011). Guava fruit contains nutrients, vitamins, and antioxidant compounds (Puspaningtyas 2012), while guava leaves contain flavonoids, alkaloids, triterpenoids, tannins, and essential oils (Agustina *et al.* 2018). The flavonoids and essential oils contained in the guava plant have antimicrobial properties so that they can be used as anti-acne (Maysarah *et al.* 2016).

Citrus plants are grown all over the world and the plant is consumed as fresh fruit, but in some countries such as Brazil and the United States parts of the plant are marketed in the form of concentrated juice or through the pasteurization process (Vand & Abdullah 2012). Lime fruit (*Citrus aurantifolia*) is used for lemonade, mixed drinks, bottled juices, and carbonated drinks. Lime fruit is also used as a flavoring and cosmetic preparation (Khan 2007). This fruit contains potassium, iron, phosphorus, calcium, vitamin C, niacin, riboflavin, B2, thiamin, B1, vitamin A, crude fiber, carbohydrates, fat, and protein (Reuther *et al.* 1967). The skin of the fruit contains essential oils which are used in the perfume chemical industry, while in the health sector, it is used as an antioxidant (Asmah *et al.* 2020). Orange juice contains saponins and flavonoids, namely hesperidin (hesperetin 7-rutinoside), tangeretin, naringin, eriocitrin, and eriocitric acid (Aprioku & Briggs 2018). Lime fruit is generally used by the industry to produce lime juice and lime powder (Abrahimiy & Haji Vand 2004).

This study combines guava and lime fruit to obtain an optimal therapeutic effect as a peel-off preparation used for facial treatments. The purpose of this study was to identify the flavonoid compounds contained in guava (*Psidium guajava*) and lime (*Citrus aurantifolia*) and the best concentration as a peel-off mask preparation.

2 MATERIALS AND METHODS

The materials used are guava fruit, lime fruit, propylene glycol, nipagin, nipasol, aquadest, 96% ethanol, magnesium, concentrated HCl, and pH paper. Experimental research design made three peel-off mask formulas, each formula with three replications.

Identification of flavonoids: 0.5 g of the sample was added with 10 ml of aquadest then heated, filtered, and 1 ml of the filtrate was taken, then added with 1 ml of 96% ethanol, 0.1 g of magnesium, and 10 ml of concentrated HCl. Flavonoids in guava and lime are indicated by the formation of orange to red color (Ministry of Health of the Republic of Indonesia 1977).

Making Peel-Off Masks: Nipagin and nipasol were added with 2 drops of 96% ethanol, added propylene glycol, and stirred continuously until dissolved. The juice of the guava fruit is added little by little, including the juice of the lime, and aquadest is added to a volume of 30 ml.

Evaluation of pH: Take a sample of a peel-off mask, put it on litmus paper, observe the color change that occurs, and then compare the color with the indicator. Evaluation of density: The clean and dry pycnometer was weighed, the sample was put in the pycnometer at a temperature of 25°C, then the sample was allowed to stand until a temperature of 20°C, and finally the temperature was set back to 25°C. Weigh the pycnometer and peel-off mask sample, record the weighing results, and calculate the density. Evaluation of viscosity: The peel-off mask sample was inserted by a viscometer to the specified limit, pulled the sample using filler to the upper limit, calculated the time required for the sample to drop to the lower limit using a stopwatch, and calculated the peel-off mask viscosity. Evaluation of homogeneity: The peel-off mask was put in a 10 ml test tube and observed using a sodium lamp and a black cloth background. The test is carried out by observing the preparation including particles or deposits in the preparation made. If there are no solid particles or deposits, the preparation is said to be homogeneous.

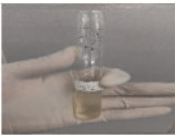
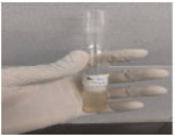
The measurement of the significant difference between the formula or the concentration of guava and lime juice with different densities and viscosity was carried out by using one-way ANOVA statistical analysis.

3 RESULT AND DISCUSSION

3.1 Identification of flavonoids

The results of the screening test showed that guava and lime fruit contained flavonoid secondary metabolites (Table 1).

Table 1. Phytochemical screening of guava and lime fruit flavonoids.

Fruit Type	Reagent	Color Change	Results
Guava	0.5 g sample + 10 ml aquadest + heat + filter and take 1 ml filtrate + 1 ml 96% ethanol + 0.1 g magnesium + 10 ml HCl	 Orange – Red	(+) Flavonoids
Lime Fruit	0.5 g sample + 10 ml aquadest + heat + filter and take 1 ml filtrate + 1 ml 96% ethanol + 0.1 g magnesium + 10 ml HCl	 Orange – Red	(+) Flavonoids

The flavonoid test used the Wilstater method by adding concentrations of Mg and HCl into the sample. The addition of HCl aims to hydrolyze flavonoids into aglycones through the hydrolysis of O-glycosyl. The glycosyl is replaced by H⁺ from the acid due to its electrophilic nature. Reduction with concentrated Mg and HCl produces orange or red-colored complex compounds which are flavonoid derivatives including flavonols, flavanones, flavanonols, and xanthenes. Flavonoids are phenolic compounds widely distributed in plants and have pharmacological properties such as antimicrobial and exogenous antioxidants (Hu *et al.* 2003, Kuber *et al.* 2013).

3.2 Making peel-off masks

The characterization of peel-off masks is shown (Table 2):

Table 2. Peel-off mask characterization.

Component	Concentration (%)				
	Formula			Standard	Literature
	I	II	III		
Guava juice (<i>Psidium guajava</i>)	9	7	5	–	–
Lime juice (<i>Citrus aurantifolia</i>)	5	7	9	–	–
Propilenglikol	12	12	12	<15	(Rowe <i>et al.</i> 2009)
Nipagin	0,2	0,2	0,2	0,02-0,3	(Rowe <i>et al.</i> 2009)
Nipasol	0,05	0,05	0,05	0,01-0,06	(Rowe <i>et al.</i> 2009)
Aquadest	Ad 30 ml	Ad 30 ml	Ad 30 ml	–	

The three formulas had the same concentration of propylene glycol, nipagin, and nipasol, but the concentrations of the active substances from guava and lime juice were different in each formula.

3.3 Evaluation

Table 3. Evaluation of pH, density, viscosity, and homogeneity.

Formula	Evaluation			
	pH	Density (g/ml)	Viscosity (cP)	Homogeneity
I	5	1,033	1,723	Homogeneous and no sediment
II	5	1,031	1,311	Homogeneous and no sediment
III	5	1,030	1,292	Homogeneous and no sediment

The pH test results (Table 3) showed that the different concentrations in the three formulas had a constant pH of 5 and met the skin pH requirements. The pH of topical preparations should be in the skin pH range of 4–7, this is due to avoid skin irritation. The more acidic or alkaline a substance is, the greater the damage caused to the skin, such as dry skin, cracks, sensitive skin, and easy infection. The pH of the preparation can change during storage, this is because the carbohydrates contained in the preparation can be digested by microorganisms so that it will undergo a complex reaction so that it will form alcohol and carbon dioxide.

The results of the density test showed that formula I had the highest density, followed by formula II, and formula III. This density is influenced by the atomic mass of a compound such as water, glycerin, bio-resin ratio, temperature, and time. Formula I concentration of guava juice is higher than lime juice, guava contains essential oils, resins, and oxalic acid compounds, besides the content of vitamin C, pectin, and fiber is higher than lime. This resulted in the density of formula I being higher than that of formulas II and III.

Table 4. Peel-off mask density ANOVA test.

	Sum of Squares	df	Mean Square	F	Sig
Between Groups	.000	2	.000	1.345	0.329
Within Groups	.000	6	.000		
Total	.000	8			

The results of the ANOVA test showed in Table 4 that the different concentrations of guava and lime juice did not affect the density of the peel-off mask preparation with a significance value of $p = 0.329$ ($p > 0.05$).

The results of the viscosity test showed that formula I had the highest viscosity, followed by formula II, and formula III. Guava contains a lot of carbohydrates, in water carbohydrates will form a gel through a helical structure due to hydrogen and ionic bonds so that there is an increase in viscosity. The viscosity of a liquid is a measure of its resistance to flow, the higher the viscosity the greater the resistance. Formula I concentration of guava juice is higher than lime juice, so the higher the increase in gelling agent which causes the viscosity of the preparation to increase and it is increasingly difficult to pour from the container. Formula II concentration of guava juice is the same as lime juice so it has a lower viscosity which makes the preparation easier to pour from the container. Formula III concentration

of guava juice is lower than lime juice so it has the lowest viscosity which makes the preparation very runny. The best formula in this peel-off mask preparation is formula II which has ideal viscosity with the same concentration of guava and lime juice.

Table 5. Peel-off mask viscosity ANOVA test.

	Sum of Squares	df	Mean Square	F	Sig
Between Groups	.356	2	.178	390.608	.000
Within Groups	.003	6	.000		
Total	.359	8			

The results of the ANOVA (Table 5) test showed that the different concentrations of guava and lime juice affected the viscosity of the peel-off mask preparation with a significance value of $p = 0.00$ ($p < 0.05$).

The results of the homogeneity test showed that the three peel-off mask formulas were homogeneous and there were no sediment or particles so they met the product requirements.

4 CONCLUSION

Based on the research results, guava fruit (*Psidium guajava*) and lime (*Citrus aurantifolia*) contain flavonoid compounds, and the best concentration as a peel-off mask preparation is formula II. Further research is needed for chemical evaluation and microbiological testing of *Psidium guajava* and *Citrus aurantifolia* peel-off masks.

ACKNOWLEDGMENTS

The author would like to thank the Pharmacy Study Program which has provided the facilities, equipment, and chemicals needed, laboratory staff, and P3M Politeknik Harapan Bersama which has provided funding.

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Mother's interest in stimulating the development of children aged 3–5 years at integrated service post (Posyandu) of Post 6 Gumayun

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ABSTRACT: Stimulation is an activity that provides direct stimulation to children from an early age. Stimulation will optimally involve the mother or closest family in its implementation. RISKESDAR data show that the percentages of stunting, underweight, and wasting are 30.8%, 17.7%, and 10.2%, respectively. In addition, RISKEDAR data also note that children in Indonesia experience developmental disorders (fine motor skills, gross motor skills, social skills, independence, and delays) by 19.3%. Based on a preliminary study of 10 mothers in Gumayun village, it was found that all mothers (100%) did not stimulate the development of their children. A total of five mothers handed over the stimulation of their children to the posyandu, while five mothers did not do any stimulation at all. The purpose of this study is to ascertain the mother's interest in promoting the development of children between the ages of 3 and 5. Cross-sectional descriptive research methodology was adopted. This research was conducted at Posyandu Pos 6, Gumayun Village, Tegal Regency in December 2021. The sampling technique used total sampling with a total of 30 respondents. Data retrieval using a questionnaire then carried data processing then analyzed using percentages. The result of this is based on high interest in 27 people (90%), high attention in 28 people (93.33%), high motivation in 18 people (60%), and high knowledge in 15 people (50%). It is recommended that stimulation according to age stages be done regularly so that children can achieve optimal development.

1 INTRODUCTION

The course of a child's growth and development can be used to assess their quality. The combination of genetic and environmental variables leads to this process. Environmental influences have an impact on a child's biological, physical, psychological, and social development, whereas genetic or hereditary aspects are tied to genes from both the mother and father (Yuniarti 2015).

Indonesia is a developing country and is included in the 10 highest countries with 4th rank which has the number of children under five with impaired growth and development in the world after India, which is 48.3 million, Pakistan is 10 million then Indonesia is 8.8 million (WHO, 2018; Millenium Empowerment Of Health Cadres In The Prevention And Management Of Stunting In Children In The Work Area Of The Jatnagor 275 Challenge Account Indonesia, 2018). In ASEAN, Indonesia is the second country with impaired growth and development in children under five after Laos (43.8%), which was 36.4% in 2015 (World Health Organization 2018).

Pilot programs that are carried out under strictly regulated circumstances are referred to as policies to promote child development (Araujo *et al.* 2021). In Indonesia, the government's effort to determine the growth and development of children is through the SDIDTK program. The implementers of this program are health workers (Soejiningsih 2014). According to the Guidelines for the Implementation of Child Development Stimulation, Detection, and Early Intervention (SDIDTK), stimulation is an activity to provide direct

stimulation to children from an early age in the form of basic skills that are directed to achieve optimal child development. Giving stimulation can be done by parents, caregivers, family members, and community groups (Kementrian Kesehatan RI 2016).

The results of basic health research in 2018 showed that the percentages of stunting, underweight, and wasting in Indonesia were 30.8%, 17.7%, and 10.2%, respectively. 19.3% of Indonesian children based on the data are known to have developmental disorders (fine motor, gross motor, social, independent, delay). Data from the Central Java Provincial Health Office in 2014 stated that the percentage of children who received growth and development services was 86.9%.

The results of research conducted by Cempaka Wati, Iin with the title “The Relationship of Developmental to the Development of Children Aged 0–5 Years in RW 8 Kalicari Village, Semarang City”. According to the study’s findings, 51.8% of mothers provided enough stimulation for their children, and 56.63% of those children reached the right developmental stage. The novelty and differences of research is that the researcher has 4 indicators of interest in stimulation, so as to be able to dig deeper into the dominant factors that play a role in the process of mothers wanting to stimulate the development of their children. It is advised to periodically provide stimulation based on age stages to ensure that children develop to their full potential (Wati 2016).

Based on a preliminary study conducted by interviewing 10 mothers in Gumayun village, it was found that all mothers (100%) did not stimulate the development of their children. As many as 50% of the mothers interviewed gave their children stimulation to the Posyandu, while 50% did not do any stimulation at all. Parents in this village only monitor their child’s developmental stage based on what happens naturally.

This study sought to ascertain the mother’s interest in promoting the development of children between the ages of 3–5. This research serves as a basis for understanding knowledge and attitudes to support in providing developmental stimulation to children, especially for mothers.

2 METHODS

Cross-sectional methodology and a descriptive research design were utilized in this study. All women at Posyandu Pos 6 Gumayun with children ages 3–5 comprised the study’s sample. Total sampling was the sampling method applied, and 30 respondents served as the sample size. Univariate analysis was performed to analyze the data used.

3 RESULTS AND DISCUSSION

Table 1. Characteristics of respondent.

No	Variable	F	(%)
	Education		
1	Elementary School	5	16.67
2	Junior High School	13	43.33
3	Senior High School	10	33.33
4	Diploma/College	2	6.67
	Occupation		
1	Housewife	19	63.33
2	Farmer	1	3.33
3	Civil Servant	1	3.33
4	Private employee	8	26.67

(continued)

Table 1. Continued

No	Variable	F	(%)
5	Entrepreneur Information	1	3.33
1	Ever	26	86.67
2	Never	4	13.33
	Information Sources		
1	Printed Media	2	667
2	Electronic Media	5	16.67
3	Friend	3	10
4	Medical Staff	20	66.67

The result showed that most respondents comprising 13 people (43.33%) have an education till junior high school. The respondents' with housewives are 19 people (63.33%). The respondents' current information is 26 people (86.67%) and those who received information through health workers are 20 people (66.67%).

Table 2. Frequency distribution of mother's interest to stimulate children aged 3–5 years.

No	Interest Indicator	High		Medium		Low		Total	
		Σ	%	Σ	%	Σ	%	Σ	%
1	Interest	27	90	3	10	0	0	30	100
2	Attention	28	93.33	2	6.67	0	0	30	100
3	Motivation	18	60	12	40	0	0	30	100
4	Knowledge	15	50	15	50	0	0	30	100

Change is a process that supports human growth and development. The development of tissues, the growth of organs, and the enlargement of structures and organs are changes in the physical characteristics that help muscles develop to their maximum strength and functionality. Individuals go through developmental changes based on their social, linguistic, and cognitive abilities. Our personalities and the processes that affect our growth are shaped by a variety of circumstances. Development is the qualitative transformation that occurs as a person learns new skills. Human development includes the ability to communicate with others through language and thought, the ability to form social bonds, and the creation of a distinct personality (KBBI 2008).

Interest is the psychological factor that causes someone to pay close attention to specific activities and motivates them to be done (WHO 2018). From the result of research conducted regarding the mother's interest in stimulating children aged 3–5 years out of all respondents, it was found that respondents had high because of attention (93.33%) and interest (90%). Parents must be able to create conditions to support the child's development process. Attention and interest is a process of activity carried out with desire and awareness. This attention and interest indicator has a high value because the mother has a desire so that she is encouraged to carry out stimulating activities for her child.

Most mothers (86.67%) were found to have received information about the growth and development of children and how to stimulate them. The majority of mothers (66.67%) received information through health workers at the Posyandu. However, after filling out the questionnaire, the results showed that as many as 15 mothers had high knowledge and 15 mothers had sufficient knowledge even though they had been given health information. It was found that 12 mothers had moderate knowledge even though they had been given health

information. One of the reasons mothers do not do stimulation is because they do not know the advantages and disadvantages, this relates to indicators of interest in terms of knowledge. Therefore, a mother must have an interest in supporting the development of her child (Mansyur 2019).

The higher the education, the wider the knowledge, on the other hand, when the education is low, the knowledge tends to be low. A mother who has a higher education tends to find it easier to get information from many ways, for example, through other people, print media, or electronic media, so that it can improve health and quality of life (KBBI 2008).

Klansja and Pratt mention that smartphones are effective in health services because they are easy and provide personal information (Klansja & Pratt 2012).

Kim *et al.* mention that mothers and families can benefit from the availability of resources such as homemade toys and children's books (particularly for low-income families) (Suprayanto 2011). Preschool children who do not have books and are supported by low maternal education significantly increase the chances of developmental problems (Heri *et al.* 2012).

Things that affect interest include economic status, education, and information. Knowledge is closely related to education. Interest with motivation in 60% most of the mothers have the latest education in junior high school which is 43.33% and work as a housewife (63.33%). The relationship between mother and child is the basis of the mother's motivation to pay attention to her child. Interest is a tendency that causes a person to try to find or try activities in a particular field or a tendency towards something or desire (Kim *et al.* 2021).

Nearly one in three children globally live in households that lack needs and necessities, and 356 million of these children live in extreme poverty (Kim *et al.* 2021). To achieve SDGs related to PAUD where all children should receive early childhood care, the World Bank also recommended a co-parenting program for child development in poor populations (Arriagrada *et al.* 2018).

Through the information that has been obtained, stimulation of child development can be done as early as possible. If the mother already has an interest and knows the importance of stimulation, she can ask the health worker whether the child has normal development or has a delay. After consulting with health workers regarding child development, the mother can stimulate following the directions from health workers to help children have normal development and not experience disturbances. This stimulation effort will indirectly improve the quality of health (Sonia *et al.* 2021). In addition, it also improves children's health, well-being, and quality of life, contributing to their full development (Magalhaesa-Barbosa *et al.* 2021).

4 CONCLUSION

Mother's interest in stimulating the development of children aged 3–5 years based on interest and attention is in the high category, while based on motivation and knowledge is in the medium category. For further researchers, it is hoped that it can be reference material, guideline, or consideration in conducting research related to the stimulating of child development, child growth, and development. Moreover, it is expected to improve understanding for mothers to stimulate development in children.

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Optimization of vinegar hand sanitizer gel formula with response surface methods

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ABSTRACT: Gell hand sanitizer formula needs to be optimized base such as carbopol and TEA in order to meet the standards.. The aim of this study was to optimize hand sanitizer formulations that meet SNI (i.e., Indonesia National Standards) with the study of active ingredients and the basis of a combination of carbopol and TEA. Hand sanitizers that have been made use 5% vinegar and a combination of carbopol 1, 2, and 3%, and TEA 1;1.5, and 2%. This active ingredient formula was made into a gel with the use of other ingredients such as methyl parabens, glycerin, and aquadest. The handsanitizer gel formula tested physical properties to obtain SNI standards such as organoleptic tests with five senses, pH with pH meters, viscosity with Otswald viscometer and scatter power. One way to optimize was to use the Response Surface Methods (RSM) in Design-Expert software. The results showed that the combination of carbopol and TEA had no effect on pH because it produced the same pH of 4,2. While the combination of carbopol and TEA affects viscosity and TEA with a probability value below 0,05. Optimization results using Design-Expert software showed that the best combination of carbopol and TEA was at concentrations of 0,802% and 1.6% which produces a pH of 4,2, viscosity of 10,893 cp, and scatter power of 5,249 cm².

1 INTRODUCTION

Health is an important aspect of human life (Rahmawati 2015). Efforts that can be made to maintain health are to maintain the cleanliness of the body such as washing hands. The development of COVID-19 is indeed starting to fall, but that does not mean ignoring health protocols. Hand-washing behavior has been shown to prevent a wide range of diseases (Hasanah & Mahardika 2020). Awareness of hand washing still needs to be applied. In addition, the presence of bacteria will certainly aggravate health conditions. In addition to viruses, most of these diseases can come from pathogenic bacteria that cannot be seen directly by the eye. One of the most powerful mediums for the spread of bacteria in the body is through the hands (Larasati *et al.* 2020). Although it does not significantly reduce the number of covid-19 due to various things. However, the use of hand sanitizer is one of the efforts of health protocols that have been proven to prevent the spread of bacteria 82.65% (Srikartika *et al.* 2016).

Various types of bacteria, viruses, and fungi will be easier to stick to and develop in the condition of unclean hands. The way to overcome the spread of these bacteria is to wash your hands using clean water. However, clean water alone is not enough to ensure that the bacteria will disappear perfectly from the hands that make direct physical contact with the bacteria every day. This can be overcome by washing hands using alcohol-based cleansers (Natanael 2015). Along with the development of technology, today many instant products are ready to be used for antiseptic hand sanitizers or so-called hand sanitizers (Sutrisno *et al.* 2020). Hand

sanitizer products are products that are used to kill disease germs found on the hands. Hand sanitizers generally contain 62% ethyl Alcohol, softeners, and moisturizers. The active ingredient content is alcohol which has the highest effectiveness against viruses, bacteria, and fungi and also does not cause resistance in bacteria. Alcohol itself can make your hands dry. Hand sanitizers should be equipped with moisturizers and emollients, which keep hands soft, not dry, unlike pure alcohol solutions that can cause dehydration of the skin. Hand sanitizers will generally evaporate (Wijaya 2013), so that it doesn't leave residue or make the hands sticky (Nakoe *et al.* 2020). In the manufacture of hand sanitizer products, it is also necessary to use natural ingredients that will be developed as antiseptics (Aprilia & Yanti 2019; Larasati *et al.* 2020). Natural ingredients that can be used as a hand sanitizer that can be used vinegar as an active substance (Pratama *et al.* 2015). Vinegar has an organic acid content that is acetic acid. The acetic acid content of vinegar acts as an antimicrobial that can cause loss of cell integrity and is tested to inhibit the growth of *Salmonella typhi* bacteria (Djuanda *et al.* 2019).

Response surface methods has been done as much as done by Gumbara *et al.* (2015), who optimized lipstick preparations from purple sweet potatoes (*Ipomoea Batatas L.*) with a combination of base paraffin wax and carnauba wax. Rao *et al.* (2016) made the development of a microemulsion-based gel formulation for antifungal preparations of *butenafine hydrochloride*. This study aims to find out the influence of active substances, carbopol bases, and TEA that most affect physical properties. The use of *Response surface methods* has advantages in the efficiency of formula-making by eliminating trial and error and replication. The use of vinegar as the active ingredient of gel formulations has been widely reported, but there needs to be formula optimization using RSM with the influence of carbopol and TEA bases that have not been reported.

2 MATERIALS AND METHODS

This study uses this type of laboratory experimental research by making a hand sanitizer gel formulation from vinegar. The independent variables of this study are the concentration of carbopol and TEA from the pharmaceutical laboratory (p.a Merck) used; the dependent variables are the response of optimization results, namely pH, viscosity, and scatter power and controlled variables namely vinegar concentration (5%), glycerin (20%), nipagin (0.18%) and nipasol (0.02%) used. Composite designs on surface response methods are used to optimize the effect of independent variables on responses and analyzed by a Design Expert. Based on the response of the design of the software will provide three experimental solutions with the given response. The design form is shown in Table 1.

Table 1. The variables and levels in experimental design.

		Level				
		$-α$	-1	0	1	$+α$
Carbopol	X1	0.6	1	2	3	3.6
TEA	X2	0.6	1	1.5	2	2.6

Viscosity measurements were performed on gel preparations using Ostwald viscometers. A good viscosity test is that the liquid does not flow easily and is clear (Voight 1995). The formula is made by weighing 5 grams of preparation dissolved in 20 mL aquadest in a beaker glass, Measuring with pH meters, and recording the pH (Astuti *et al.* 2017). The scatter power test is conducted to ensure the distribution of gel when applied to the skin as soon as the gel is made. The gel is weighed as much as 0,5 g and then placed in the middle of a round glass scale. On the gel is placed another round glass or other transparent material and ballast so that the weight of the glass is round and ballast 150 g, let stand for 1 minute, then record the diameter of the spread. Good gel scattering power between 5 and 7 cm (Mappa *et al.* 2013).

3 RESULTS AND DISCUSSION

The experimental results were shown from the results of the software analysis presented in Table 2. Modeling with significant values R2 and lack of fit values of each response with a specific pattern suggested software. After that, the model is optimized with a target.

Table 2. The experimental design for optimizing the formula.

STD	Run	Variables				Responses		
		Code	Actual (Carbopol %)	Code	Actual (TEA %)	pH	Viscosity (Cp)	Scatter power (cm)
1	1	-1	1	-1	0.6	4.2	10.279	5.25
11	2	0	2	0	1.5	4.2	11.002	5.3
10	3	0	2	0	1.5	4.2	10.809	5.25
7	4	0	2	-1.41421	0.6	4.2	10.935	5.25
8	5	0	2	1.41421	2.6	4.2	9.638	5.2
5	6	-1.41421	0.6	0	1.5	4.2	10.71	5.17
13	7	0	2	0	1.5	4.2	10.968	5.25
12	8	0	2	0	1.5	4.2	10.214	5.32
6	9	1.41421	3.6	0	1.5	4.2	10.935	5.25
3	10	-1	0.6	1	2	4.2	11.002	5.31
4	11	1	3	1	2	4.2	11.079	5.25
2	12	1	3	-1	1	4.2	9.638	5.21
9	13	0	2	0	1.5	4.2	10.809	5.25

Hand sanitizer gel preparations are made by means of gelling agents (carbopol and TEA) developed by aquadesting 70°C in a chemical glass, stirring it until it expands. Then, TEA was mixed into the base of the gel and then homogenized. Add nipagin and nipasol that have previously been dissolved with 3 ml of aquadest at 90°C, homogenizing. Dissolve the vinegar into glycerin, then put it into a little base at a time, homogenizing. Then add the rest of the aquadest after it homogenizes (Syaiful 2016).

In the research that has been done, the preparation consists of thirteen formulas of gel hand sanitizer with base concentrations (carbopol and TEA) in accordance with the results of running the software. The physical evaluation response of hand sanitizer gel preparations includes pH, viscosity, and scatter power to be analyzed for modeling. The response of these physical properties is shown in Table 3:

Table 3. The analysis of variance from the analysis shows the effect of all factors ($p \leq 0.05$).

Factors	p-value dependent variables		
	pH	Viscosity	Scatter power
Model	Mean	Quadratic	2FI
A-Carbopol	0.000	0.1572	0.8676
B-TEA	0.000	0.0096	0.1773
AB		0.0958	0.2561
A2		0.1518	
B2		0.1988	
Lack-of-fit	0.000	0.615	0.9844

*Significantly different at a 95% confidence level

The equations for the model on each parameter are presented below:

$$\text{pH} = +4.20$$

$$\text{Viscosity} = 10.60 - 0.18A + 0.40B + 0.31AB + 0.19A^2 - 0.17B^2$$

$$\text{Scatterpower} = 5.25 + 2.500E - 003A + 0.021B + 0.025AB$$

Based on the equations, (A) was the Carbopol response, (B) was the TEA response, and the combination of Carbopol and TEA (AB), as well as the values of double Carbopol (A²) and TEA (B²); the synergistic effect was represented with positive marks in front of the equation, and opposition was represented with minus (Ulfa *et al.* 2021).

Instead of an antagonistic effect. The results of pH observations of hand sanitizer gel preparations on the basis of a combination of carbopol and TEA for thirteen formulas in Table 2 showed a pH of 4.2. These results showed that the combination of carbopol and TEA had no effect on the pH of the preparation.

The scatter power shown in Table 2 showed that of the thirteen formulas with a combination of carbopol base and TEA has the highest scatter power of 5,32 cm². Furthermore, statistical processing is carried out with the Response Surface Method with a composite design that aims to find out the influence of both factors (carbopol and TEA) on the power response of the hand sanitizer gel spread. Calculations based on 2FI modeling obtained from the software showed that the combination of carbopol and TEA showed from the equation with the highest coefficient value of 0.025 exerted the most influence on the results of the scatter power test when compared to the more dominant concentration of either TEA or carbopol.

The above results show that the combination of carbopol and TEA is modeled with quadratic with the equation result has the largest coefficient value of 0.4B which means the concentration of carbopol exerts the most influence on the viscosity test results when compared to one of tea and combination of both.

The effect of free variables against each solution based on modeling is presented in Table 4. Modeling results provide three solutions based on validation in the laboratory. Optimization validation results using design expert software show that the best combination of carbopol and TEA is at concentrations of 0.802% and 1.6% which produces a pH of 4.2; viscosity 10.893 cp and scatter power of 5.249 cm².

Table 4. The three solutions were obtained from the software.

Solutions	Independent Variables		Dependent Variables		
	Carbopol (%)	TEA (%)	pH	Viscosity	Scatter power
Solution 1	0.802	1.6	4.2	10.893	5.249
Solution 2	3	2	4.2	11.148	5.300
Solution 3	2	1,5	4.2	10.603	5.251

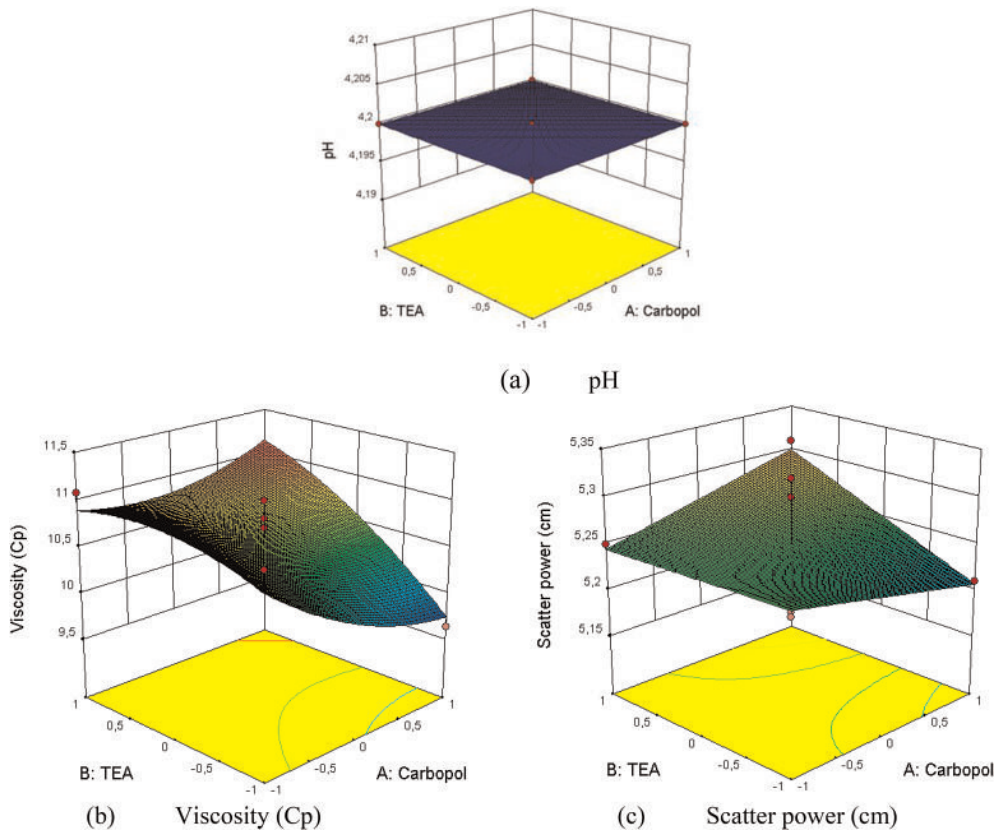


Figure 1. All 3D graphs showing the influence of carbopol and TEA concentration (a) pH, (b) viscosity, (c) scatter power.

4 CONCLUSION

The combination of carbopol and TEA had no effect on pH because it produced the same pH of 4.2, whereas the combination of carbopol and TEA affects viscosity and TEA with a probability value below 0.05. Optimization results using design expert software showed that the best combination of carbopol and TEA was at concentrations of 0.802% and 1.6% which produces a pH of 4.2, viscosity of 10.893 cp, and scatter power of 5.249 cm².

ACKNOWLEDGMENT

This research was financed by the Funds of Politeknik Harapan Bersama through the P3M Unit.

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Predictors of preventive behavior against COVID-19 among people living in the suburban area a year after pandemic

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ABSTRACT: Corona Virus Disease 19 (COVID-19) has dramatically impacted people's lives by its uncertainty. While preventive behavior is crucial, factors contributing to adopting such behavior are varied in a specific context. This study aimed to examine predictors of COVID-19 preventive behavior of people living in suburban areas of Indonesia one year after the pandemic. A cross-sectional, correlational study recruited 246 people living in a suburban area, Tangerang, Indonesia. A form of personal characteristics, vaccine acceptance, self-efficacy, COVID-19 knowledge, and COVID-19 prevention behavior questionnaires were provided based on validity and reliability tests. Factor predictors of COVID-19 prevention behavior were analyzed by linear regression. The results revealed that age negatively predicted preventive behavior, while years of education and self-efficacy positively predicted COVID-19 prevention behavior among people living in a suburban area. 9.6 % of the variation in COVID-19 preventive behavior among people living in suburban areas could be explained by age, education, vaccine acceptance, self-efficacy, and knowledge about COVID-19. The study suggests that older age, low education, and poor self-efficacy need to be the priority group of concern in promoting the adoption of preventive behavior against the COVID-19 pandemic.

1 INTRODUCTION

Since coronavirus disease 19 (COVID-19) was declared a pandemic on 11 March 2020 by the World Health Organization (WHO Director-General's Opening 2020), it has dramatically impacted people's lives, including economic and health aspects, such as physical, mental, and social. Health measures to prevent the spread of COVID-19, including physical and social distancing, adequate ventilation, wearing a mask, hand hygiene, and quarantining, have been continuously reminded and recommended to adopt in daily life. Several guidelines have been adjusted to accommodate the application of preventive measures in the workplace, school, and other public or community facilities. However, after a year of the pandemic, 12,807 COVID-19 death cases and 787,408 new confirmed cases as of April 2021 steadily increased (Coronavirus *Pandemic* (COVID-19) 2020), which might reflect the issue of health behavior adoption as COVID-19 prevention behavior.

Moreover, the emerging injection of the COVID-19 vaccine instills hope in the people to end this pandemic's uncertainty, isolation, and negative impact. In particular, at least 5.7% population in April and 48.4% of people worldwide in October 2021 have been vaccinated for the first dose. It indicates the expectation to learn to live with the virus by changing the way of life, including willingness to get the vaccination. Nevertheless, Indonesia, a lower-middle-income country, reported a slow vaccine rate, making COVID-19 an epicenter in Asia (Zhongming *et al.* 2021). For instance, 21.7% of Indonesians have completed the total dose as of October 2021 (Coronavirus *Pandemic* (COVID-19) 2020), which requires more time and effort to cover 70% of the population to achieve herd immunity. Thus, people living

in the community is suggested to persistently apply health measure to prevent the spread of the virus while participating to get vaccine of COVID-19.

Adopting health-promoting behavior is challenging since many interrelated factors contribute to people adopting and adjusting to the new behavior in their day-to-day lives. Approximately two-thirds of people in Indonesia reported willingness to get COVID-19 (Kemenkes 2020). However, the study was an online survey and almost 70% of the respondents were middle class (Kemenkes 2020). A previous study found that some factors, such as socioeconomic, correlated with vaccine acceptance (Joshi *et al.* 2021). Hence, the willingness to accept the COVID-19 vaccine might differ from other socio-economic contexts, such as people living in a suburban community.

Moreover, the benefits of vaccination to eradicate COVID-19 are the highlight of health-promoting behavior amidst pandemic situations. However, the adoption of COVID-19 prevention behavior is still an issue even after the pandemic year. For instance, only 32 % of people reported wearing the mask, even though 57 % stated that they knew the benefit of wearing it in preventing the spread of the virus (Chavarría *et al.* 2021). Moreover, to our knowledge, vaccination acceptance studies and their correlation with COVID-19 preventive behavior are under investigation in Indonesian people living in suburban area. Hence, some concepts under Pender's Health Promotion Model (Pender 2011) and literature review were used to guide this study. Even though few studies have observed vaccine acceptance (Ardiningsih & Kardiwinata 2021; Arumsari *et al.* 2021; Puspasari & Achadi 2021), yet no further analysis in predicting the prevention behavior. Therefore, this study aimed to examine predictors of COVID-19 prevention behavior among people living in suburban areas of Indonesia a year after the pandemic.

2 METHODS

This study was a cross-sectional, correlational design. Based on Slovin's formula, the required sample was 246 people. Moreover, the current study setting was a suburban area, namely Tangerang City, Banten Province, Indonesia. Consecutive sampling was used with the inclusion criteria of age 18 and has been a permanent resident in Tangerang City. The ethical approval was granted from the Faculty of Medicine and Health, Universitas Muhammadiyah Jakarta (No. 060/PE/KE/FKKUMJ/II/2021). Since the limited internet access in the target population, the questionnaire was directly distributed to the sample by following strict health measures to prevent COVID-19 in April 2021.

Five parts of the questionnaire were used to identify personal characteristics, vaccine acceptance, self-efficacy, COVID-19 knowledge, and COVID-19 prevention behavior for data collection measurement. First, the researcher developed the form of a personal characteristic consisting of age, level of education, monthly expenditure, insurance, and social assistance from the government. Second, the COVID-19 knowledge questionnaire was adopted from Clements, Frazier (Clements *et al.* 2020). The Cronbach Alpha was 0.55, indicated as acceptable. The third, the Self-efficacy questionnaire, was developed by the researcher based on a literature review. It consists of three items with a 4-rating scale assessing confidence in preventing, avoiding transmission, and encountering any issue infected by COVID-19. The Chronbach Alpha was 0.72, representing good reliability. For the vaccine acceptance, it is a single item, 4-point rating scale asking, "Considering the costs and benefits, how likely would you be to voluntarily get the coronavirus vaccine if it were available to the public?" The last questionnaire of COVID-19 Prevention Behavior was modified from Melesie Taye, Bose (Melesie Taye *et al.* 2020). It is 13 items with a 4-point rating scale with a higher score indicating the better performance of prevention behavior. The Chronbach Alpha was 0.76 represents good reliability.

Concerning the data analysis, descriptive analysis was performed to measure the frequency and percentage of personal characteristics, including age, level of education, monthly

expenditure, insurance, and social assistance. Mean, standard deviation, and range were used to measure continuous data from COVID-19 knowledge, vaccine acceptance, self-efficacy, and prevention behavior. Moreover, linearity, no multicollinearity, and independent observation assumptions were met prior to linear regression analysis.

3 RESULTS

Table 1. Characteristics of people living in suburban areas of Indonesia one year after COVID-19 pandemic (n = 246).

Characteristics	n	%
Age		
Late Adolescents (<20 year)	147	59.8
Adults	76	30.9
Middle-age & aging	23	9.3
Level of Education		
Low	200	81.3
High	46	18.7
Monthly Expenditure		
< 1.2 million IDR	160	65
1.2 – 6 million IDR	52	21.2
>6 million IDR	34	13.8
Insurance		
Insured	171	69.5
Uninsured	75	30.5
Social Assistance		
Yes	106	43.1
No	140	56.9

Out of 246 participants, half were late adolescents (59.8%), had a low level of education, had monthly expenditures <1.2 million IDR (65%), were insured by Universal Health Coverage (69%), and had not received social assistance from the government (56.9%). Moreover, the average age of the participant was 28.33 and the average years of education were 12.32. In this study, the most frequent adoption of preventive behavior was washing hands (84.1%), followed by wearing a mask (83.7%), physical distance (78.1%), consuming nutritious food (77.2%), and (74.8%) staying at home when sick (Table 2). For acceptance of vaccination, the mean score was 3.15 and SD = 0.93, with a high average score of self-efficacies, vaccine acceptance, COVID-19 knowledge, and COVID-19 preventive behavior (Table 3).

Table 2. Covid-19 preventive behavior frequently performed by people living in suburban areas.

Item	%
Wearing face mask when going out	83.7
Using public transportation	21.9
Avoiding the crowd	60.9
Washing hand frequently	84.1
Maintaining physical distance	78.1
Consuming nutritious and healthy food	77.2
Exercise regularly	30.5
Consuming herbal supplements	34.5
Consuming vitamin and zinc	52.4
Not shaking hands	65.9
Staying at home when sick, unless need medical care	74.8
Increasing physical activity than before pandemic	37.8
Complying with the recommended diet	22.8

Table 3. Descriptive statistics of vaccine acceptance, self-efficacy, COVID-19 knowledge, and COVID-19 preventive behavior.

Variables	M	SD	Range
Vaccine acceptance	3.15	0.93	1–4
Self-efficacy	10.22	1.82	3–12
COVID-19 knowledge	17.47	1.79	11–22
COVID-19 preventive behavior	35.67	5.86	19–49

Table 4. Multivariate regression analysis of COVID-19 preventive behavior.

Model	b	SE	Beta	t	p-value
Age	−0.07	0.03	−0.13	−2.13	0.034
Years of education	1.03	0.44	0.14	2.31	0.022
Self-efficacy	0.81	0.21	0.25	3.9	0.000
Vaccine acceptance	−0.11	0.41	−0.01	−0.27	0.784
COVID-19 knowledge	0.12	0.2	0.03	0.63	0.527

Dependent variable: COVID-19 Preventive Behavior

Constant = 23.44, $R^2 = 0.111$, Adjusted $R^2 = 0.096$, $F(5, 240) = 5.992$, $p < 0.001$

Table 4 revealed that factors significantly influencing COVID-19 preventive behavior were self-efficacy (Beta = 0.25, $p < 0.001$), followed by years of education (Beta = 0.14, $p < 0.05$), and age (Beta = −0.13, $p < 0.05$). All variables in the regression model explained a 9.6% variance of COVID-19 preventive behavior in this study. The predicted equation is:

COVID-19 Preventive Behavior' = 23.44 − 0.13age + 0.14yearseducation + 0.25self-efficacy − 0.018vaccineacceptance + .039COVID − 19Knowledge.

4 DISCUSSION

Three factors, including age, years of education, and self-efficacy, significantly influenced COVID-19 preventive behavior among people living in suburban areas in Indonesia. It was found that the most vital factors that contributed to COVID-19 preventive behavior were self-efficacy, followed by education, and age. The findings imply that good prevention behavior against COVID-19 was influenced by the better perception of people regarding confidence in preventing COVID-19 and managing the spread of the virus through any resources.

For the age, it was negatively influenced COVID-19 preventive behavior. It indicates that older participants were less likely to perform COVID-19 preventive behavior. The study revealed that most participants were late adolescents (< 20 years old). As Gutu, Leges (Gutu *et al.* 2021) found similar characteristics of age with the present study; they reported that younger age was more prevalent in using social media and tended to show good preventive behavior against COVID-19. In a pandemic situation, advanced age are more likely to decline protective behavior since they tend to engage more in performing routine activities at home and have less contact with the crowd in public or health facilities amidst COVID-19 (Pasion *et al.* 2020). It might be because younger people find it easier to access health information from social media regarding preventive behavior than older people living in the community.

Concerning years of education, it shows that people living in a suburban area with longer years of education were more likely to adopt preventive behavior. A high level of education was more prevalent than low education in this study, with an average of 12 years of secondary education. The findings confirmed the study of Bazaid, Aldarhami (Bazaid *et al.* 2020) stated that higher education positively correlated with behavior practice to prevent COVID-19. It might be because a higher level of education could facilitate people to access more information related to COVID-19 and help them understand the provided health information better to adopt in their lives. However, the findings are inconsistent with the study of Alagili and Bamashmous (Alagili & Bamashmous 2021), which reported that higher education was less likely to perform COVID-19 preventive behavior due to a lack of complete understanding of skepticism. The possible reason to explain this was the previous study conducted at the beginning of the COVID-19 situation, which might affect how people with higher education perceived information about the pandemic, and lack of trust in circulated information about the unfamiliar situation, leading to poor adherence to recommended preventive behavior. Meanwhile, this study evaluated the adoption of COVID-19 preventive behavior a year after the pandemic, which might reflect the difference in people's perception to the preventive behavior against COVID-19.

Self-efficacy made the most substantial unique contribution in explaining COVID-19 preventive behavior concerning self-efficacy. The results indicate that the higher self-efficacy in preventing COVID-19 is perceived by the people living in a suburban area, the more likely they will adopt the preventive behavior. It could happen because the perception of the ability to encounter problems, such as preventing COVID-19, could help people adopt new healthy behaviors to prevent COVID-19. As Pender believes that behavior-specific cognition, such as self-efficacy increase the probability of commitment to perform specific action then influence healthy behavior (Pender 2011). The findings were consistent with (Ab Malik *et al.* 2021; Mahmood *et al.* 2021; Wungrath & Autorn 2021). It confirms the findings of Ab Malik, Mohd (Ab Malik *et al.* 2021) in Malaysia. Hence, the belief that individuals can enact a behavior is crucial to executing specific actions to achieve the desired outcome.

Noteworthy, it was found that 9.6 % of the variance of COVID-19 preventive behavior could be explained by age, years of education, self-efficacy, vaccine acceptance, and COVID-19 knowledge. This result was higher than the previous study in Indonesia, which reported a 7% variance in COVID-19 preventive behavior (Purba & Barimbing 2020). Nursing is an important paradigm for underpinning care for patients, and so, understanding the concepts of the person (patient), health, nursing, and environment is essential for maintaining the quality of nursing care (Elon *et al.* 2021). For instance, the current study discovered that age, years of education, and self-efficacy are internal factors that influence preventive behavior. It indicates that other factors need to be explored and examined to predict COVID-19 preventive behavior better. Moreover, it was found that knowledge about COVID-19 was not a significant predictor of preventive behavior, and vaccination acceptance was negatively associated with COVID-19 preventive behavior though it was not statistically significant. It indicates that the higher acceptance rate of vaccination is more likely to decline preventive behavior adoption. It could be a concern for policymakers and healthcare providers to consider innovative strategies in promoting COVID-19 preventive behavior even more in the future since the vaccination program is still administered globally and nationally.

5 CONCLUSION

This study applied Pender's Health Promotion Model to examine factors influencing COVID-19 preventive behavior a year after the pandemic among people living in suburban areas in Indonesia that might have different contexts and have not been explored in

previous studies. People with younger age, higher education, and perceived higher self-efficacy were more likely to perform COVID-19 preventive behavior. Despite its strength, this study has some limitations, including a small percentage of older adults could limit the generalization of the study's results. Moreover, this study suggests that prior to providing health promotion in the suburban community, healthcare providers need to consider characteristics of age and education, such as prioritizing groups of older age with low education for increasing self-efficacy leading to influence the adoption of COVID-19 preventive behavior.

ACKNOWLEDGMENTS

The authors acknowledge the Faculty of Health Science, Universitas Muhammadiyah Tangerang, for this study's financial support.

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Prescription off-label medicine for children at Saras Sehat Pharmacy in Tegal city

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ABSTRACT: Use that does not correspond to drug information and marketing authorization is referred to as off-label drug prescribing. The child population is particularly at risk of off-label drug prescribing due to the specificity of the condition. This study was conducted to find out how the prevalence of off-label drug use in children in Saras Sehat Pharmacy in Tegal City. This study is a descriptive study with data retrieval retrospectively. The study subjects in the form of recipes and medical record data of children aged 0–12 years in November 2021. Classification of off-label drugs is grouped with the ATC (Anatomical Therapeutic Chemical) system. Identify off-label drugs using BNFC, DIH, PDH, and IONI. The total prescribing of children during the study period was 1,495 prescriptions, a total of 368 prescriptions met the inclusion criteria. The total drug use of 368 prescribing was 2,743 drugs with 67 types of drugs. Based on the results of a study of 368 recipes found a total of 177 prescription sheets (48.10%) identified off-label. The prevalence of off-label drug prescribing categorized as off-label indications amounted to 40 (1.45%), off-label age 341 (12.43%), off-label contraindications 22 (0.80%), off-label dose 3 (0.11%), and no off-label category of route giving was found. The most widely prescribed off-label drugs are Decongestant drugs, namely Triprolidin and Pseudoephedrine as much as 124 (4.52%). Based on the results of this study it is known that off-label drug prescribing in children is still high enough that supervision related to the risk of drug use needs to be done.

1 INTRODUCTION

In the selection or drug regimen should be based on the disease, age, sex, weight, and physiology of the patient. However, sometimes doctors prescribe drugs outside the indications listed on the label, or better known as off-label drugs. Off-label drugs are drugs that are prescribed but not used according to the indicated drug indications. These discrepancies include drug indications that are not in accordance with those stated by the marketing authorization as well as dose, patient age, and route of administration (Pratiwi *et al.* 2013). One of the reasons for the use of off-label drugs is the lack of clinical response to previous treatment, contraindications to other alternative drugs such as the availability of approved drugs according to indications and patients with alternative treatments for clinical reasons (Palčevski *et al.* 2012).

Safety and effectiveness assessment is one of the key aspects of using off-label prescriptions. The FDA recognizes that, under certain circumstances, the use of off-label drug products is approved if rational, and acceptable to medical practice. In this context, it is important that doctors should have access to accurate information about the drugs used that are not as indicative or off-label (Danés *et al.* 2014)

Knowledge about off-label drugs is considered important to avoid the occurrence of medication errors or unwanted things. Drug selection in patients should be careful because

not all drugs that are not given without indications can be used, in addition to having the advantage of off-label drug use also has disadvantages. Then medical personnel, especially pharmacists, are required to have more knowledge about drugs.

Before considering the off-label drugs used, safety support aspects and evidence of efficacy need to be evaluated to determine the risks and benefits that occur, especially drugs that have been approved by BPOM. Considering or reviewing the use of off-label drugs, health worker or medical personnel must be based on existing scientific evidence (evidence based) related to rational drug use.

The use of off-label drugs in Indonesia itself still has little evidence of prevalence data as well as known existence of its use. In a previous study, it was explained that the use of off-label drugs in prescribing acute respiratory infections was 23% in pediatric patients. One of the pharmacies in Tegal district that has a pediatrician practice is Saras Sehat pharmacy, where many pediatric patients carry out examinations at the site. Therefore, this study will identify how many off-label drug prescriptions in Indonesia, especially pediatric patients at the Saras Sehat Pharmacy in Tegal Regency.

2 METHODS

This research is an observational study with retrospective data collection in the form of prescriptions from pediatricians. This study reviews or examines off-label drug prescribing and patterns of use. Identification of prescribed drugs including off-label categories or not based on the Drug Information Handbook, Pediatric Dosage Handbook, British National Formulary Children's, and the Indonesian National Drug Informatory. This research was carried out at the Saras Sehat Pharmacy, Tegal Regency, with a period of three months to collect research data, from October to December 2021. The population in this study is all prescriptions for pediatric patients for the period of November 2021 that were prescribed by Pediatricians at the Saras Sehat Pharmacy, Tegal Regency that met the inclusion and exclusion criteria. The population of children's prescriptions for the November 2021 period amounted to 1,495 prescription sheets, and those who met the inclusion criteria were 368 prescription sheets. The sample in this study was all population prescriptions for pediatric patients at the Saras Sehat Pharmacy, Tegal Regency for the period November 2021, which met the inclusion criteria. The sampling technique was carried out using the Total Sampling method, where all members of the population who had met the requirements were used as samples. Inclusion and exclusion criteria in the population and sample of this study are as follows:

2.1 *Data analysis*

Analysis of the data in the form of patient demographic data, drug use profiles, drug categories based on ATC and off-label drug prescriptions for indication categories, age, dose, contraindications and route of administration are presented in the form of tables and diagrams. Off-label drug identification refers to the reference DIH, PDH, BNFC, IONI. Conclusions were drawn to determine the prevalence of off-label drug prescribing by percentage of what off-label categories were used the most.

3 RESULTS AND DISCUSSION

In this study, the population of children's prescriptions for the November 2021 period was 1,495 prescription sheets. According to the inclusion criteria, 368 prescription sheets were obtained, and 1,127 prescription sheets were excluded from the study because the patient's age data were incomplete. Recipes that met the inclusion criteria were used as samples.

The results of the study found that the number of male patients was more dominant (52.99%) than girls (47.01%). The dominance of patients aged under five (aged 0–5 years) was greater, namely 271 patients (73.64). Basically, the age of toddlers as a stage of development is quite vulnerable to various diseases. Several factors that trigger disease in toddlers include the structure and anatomy of the body's organs, the immune system is excessive so that it is easy to have allergies or deficiencies so that it is easy to become infected, infectious diseases that are not treated properly, genetic factors and geographical conditions.

3.1 Disease diagnosis

The results of the observation found that the distribution of disease diagnoses was ARI (25.54%), bronchitis (11.41%), diarrhea (11.41%), asthma (11.14%). The population of children is susceptible to respiratory tract diseases due to infection with pathogens (bacteria and viruses) and allergens.

Table 1. Characteristics of research subjects.

NO	Patient Characteristics	Amount (%)
1	Gender	
	Man	195 (52.99%)
2	Woman	173 (47.01%)
	Age	
	0 – 5 years	271 (73.64%)
	5.1 years – 12 years	97 (26, 36%)

The percentage of children aged 1–5 years is more likely to go to the clinic than children aged 6–12 years and more boys than girls (Table 1). This is because children aged 1–5 years are more susceptible to infection than children aged 6–12 years. In general, children aged 1–5 years have a low immune system compared to older children (Yuan *et al.* 2017). In infants to toddlers, ARI is generally the first occurrence of infection and the immune process has not been formed optimally so that immunity not perfect. In addition, children under five often put something in their mouth that can be an intermediary for the entry of germs into the body (Maakh *et al.* 2017).

Based on the diagnostic data, the tendency for male patients is more often to develop respiratory tract diseases. Sex differences in the incidence of respiratory disease vary, depending on age and differences in biological characteristics. The role of genetics is very important in influencing the immune system, especially at an early age. The number of X chromosomes in women is more than in men, thus affecting the amount of micro-RNA that plays an important role in immunity. Another factor is that boys tend to be more active than girls so that they are more likely to be exposed to the causative agents of ARI. The incidence of respiratory disease in boys aged 2–5 years is 2 times more often than girls.

The results of our study are in line with the research of Maakh *et al.* as well as the results of Sujata Jadhav's study where non-pneumonia ARI patients were more common in boys aged 1–5 years than girls.

3.2 Distribution of patient drug use

During the study, from 368 prescription sheets, 67 items were found with a total use of 2,743 times. The drug with the most use was Cefixime (10.93%) which was indicated as an antibacterial. Cefixime is a third-generation cephalosporin broad spectrum antibiotic used to

treat a number of bacterial infections such as otitis media, urinary tract infections, strep throat, pneumonia, gonorrhea, and Lyme disease.

3.3 Classification of drugs based on the ATC system

The use of drugs is then grouped based on the ATC (Anatomical Therapeutic Chemical) system, which is the system used to classify drugs. This system divides drugs into different groups according to the organ or system in which they provide activity or the therapeutic and chemical characteristics of the drug (Rishoej *et al.* 2018).

From the results of the analysis based on the ATC system, the highest drug prescription was for the respiratory system drug category (34.63%). This result is in accordance with the data on the diagnosis of the disease that most patients suffer from, namely respiratory tract diseases. At the age of toddlers are very susceptible to respiratory tract diseases such as ARI, bronchitis, asthma, common cold and pharyngitis. Basically, toddlers are quite vulnerable to the emergence of various kinds of infectious diseases. This is associated with the structure and anatomy of organs and the immune system that is not yet fully developed. Cyproheptadine, Triprolidine, Pseudoephedrine was more dominantly prescribed, followed by Erdosteine HCl, Procaterol HCl, Cetirizin HCl and Ambroxol. The drug prescribing profile is in accordance with the dominance of the disease diagnosis, namely ARI.

Cyproheptadine is an antihistamine drug that is of great use in the treatment of nasal allergies, allergic rhinitis, to relieve red eyes, watery eyes, irritation, itching, sneezing, and runny nose caused by allergies, airborne irritation, and fever. Triprolidine and Pseudoephedrine are decongestant drugs that can be used to treat nasal congestion symptoms in cases of flu or colds, as well as other respiratory diseases. Erdosteine HCl belongs to the class of mucolytic drugs, namely drugs that are useful for thinning phlegm. Usually, this drug is used to treat acute cough symptoms in people with chronic bronchitis. Procaterol HCl is a drug to treat shortness of breath due to asthma and Chronic Obstructive Pulmonary Disease or COPD. Ambroxol is a medicine to relieve cough with phlegm caused by several conditions, such as bronchitis or emphysema. In conditions of cough with phlegm caused by a bacterial infection, the use of ambroxol can be combined with antibiotics (Trisnawati *et al.* 2017).

3.4 Off-label drug prescribing characteristics

Based on research from a sample of 368 prescriptions, which were identified off-label were 177 prescription sheets (48.10%) and on-label were 191 prescription sheets (51.9%) (Figure 1).

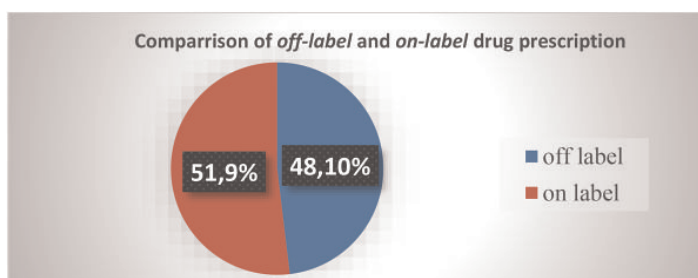


Figure 1. Number of comparisons of off-label and on-label prescriptions.

Category off-label indication (1.46%), off-label age (12.43%), off-label contraindication (0.80%), off-label dose (0.11%).

3.5 Category off-label indication

The most dominant use of off-label indicated drugs in children in this study was Ondansetron, which was 26 cases. Ondansetron is an anti-emetic drug class 5-HT₃ blocker that works by blocking serotonin in the body to prevent nausea and vomiting. Some guidelines do not recommend antiemetics for the management of gastroenteritis in children. This is due to concerns about the side effects of anti-emetic drugs, namely sedation, extra pyramidal reactions, and diarrhea. Food and Drug Administration (FDA) also only recommends ondansetron to prevent and treat vomiting due to chemotherapy.

Cyproheptadine is used to relieve allergies, such as in cases of allergic rhinitis, allergic conjunctivitis, and mild allergic manifestations of the skin such as urticaria and angioedema. Cyproheptadine is also used in cases of vascular migraine (Ping 2019). Cyproheptadine is often used off-label to stimulate appetite and weight gain in children and adults; but only a few indications for clinical use (Indonesia 2016).

3.6 Category off-label age

In this study, the off-label age category was the dominant one. Most pediatric patients get drugs with restrictions on use for a certain age. Types of decongestant and antihistamine drugs (Triprolidin, Pseudoephedrine, and Cyproheptadine) are drugs with restrictions on use for children under 6 years. Meanwhile, according to DIH (Fatmawati 2014) Triprolidine, Pseudoephedrine and Codeine are not intended for children under 2 years of age. The use of Triprolidin in children can cause hallucinatory effects.

Triamcinolone is a corticosteroid drug class as anti-inflammatory in various medical conditions, such as allergies, asthma, various skin diseases, adrenal insufficiency, and symptom relief in arthritis. Corticosteroids are used for the management of reversible and irreversible airway disease. British National Formulary of Children limits the use of triamcinolone for children less than 6 years. Some unwanted side effects if long-term use is that it can cause growth retardation in children and affect pubertal development. Long-term use of corticosteroids can increase susceptibility to infection and exacerbate or worsen the infection (Turner *et al.* 1998).

Salbutamol is also a drug within a certain age limit. Salbutamol is a beta-2 agonist drug that plays a role in the management of asthma or chronic obstructive pulmonary disease (COPD). Therapy with oral bronchodilators is not recommended in children because of the slower onset of action and the higher incidence of side effects compared to the inhalation route. Although the risk of ingestion is small, the side effects of oral salbutamol that may occur in children are hypokalemia, hypoglycemia, restlessness, tremor, tachycardia, and peripheral vasodilation (Cholisoh & Rohmah 2020). The British Medical Association and the Royal Pharmaceutical Society of Great Britain state that oral salbutamol is not recommended for children younger than 3 years and intravenously is not recommended for children younger than 12 years. IONI states that the efficacy of Salbutamol for children aged <18 months is still in doubt.

Codeine is an opioid that is widely used for both analgesic and antitussive. Codeine has a detrimental effect that is fatal for pediatric patients, this is due to polymorphisms in the gene that metabolizes codeine. The UM (Ultrarapid Metabolizer) gene causes high levels of morphine in the patient's blood, causing respiratory depression and death. Therefore, the use of codeine in children is not recommended and the drug should be replaced with other drugs that are safer for pediatrics, namely Levodopropofizine and Mogueisteine.

Cyproheptadine is a first-generation antihistamine and serotonin antagonist with anticholinergic effects. This drug is mainly indicated as an antiallergic drug with mild complaints, such as allergic rhinitis and cold urticaria, and can be used for migraines. Cyproheptadine is only recommended for use in children aged 2 years and over. A significant side effect of cyproheptadine is central nervous system depression (Najib *et al.* 2014).

Dextromethorphan is a cough suppressant. This drug works by inhibiting the response or cough reflex in the brain. Please note that this drug is not effective for relieving cough with phlegm or cough caused by chronic bronchitis, asthma, emphysema. The main indication for dextromethorphan is as an adult antitussive in conditions associated with infection or allergies, such as upper respiratory tract infections (ARI). Use as an antitussive in children is not recommended, the use of dextromethorphan in children has not been proven effective and causes side effects of nausea, gastrointestinal disturbances, drowsiness, and dizziness.

3.7 *Category off-label contraindications*

Loperamide works by reducing bowel movements so that it stops diarrhea, in adults this mechanism may be used because the immune system is already good, but in children it is dangerous, because basically the cessation of bowel movements causes the viruses/bacteria that cause cannot get out of the body and can cause some things like fever and viral/bacterial growth becomes excessive. In addition, children's gastrointestinal nervous system that is not yet perfect will also be at risk of prolonged 'limp' due to this drug and cause paralytic ileus, and in some cases can 'skid' causing a condition called intussusception/invagination which is very dangerous.

3.8 *Category off-label dosage*

Cefixime is indicated for the treatment of uncomplicated urinary tract infections, pharyngitis, tonsillitis, acute bronchitis and acute exacerbations of chronic bronchitis and uncomplicated gonorrhea with different doses for adults, children, and special populations. The general recommended dose for oral use is as a single dose once daily, or in 2 divided doses every 12 hours (twice daily). The results of the study found 3 cases of off-label doses or about 0.11% of the use of Cefixime, namely its use 3 times a day, not according to the dosage/rules of use recommended in the brochure or approved label (Indonesia 2016).

The use of off-label drugs is generally carried out by doctors with a note if there is no standard dosage or use to treat certain diseases or if the standard treatment that has been carried out is not successful. The use of off-label drugs must be based on strong scientific evidence, especially regarding the evaluation, efficacy and safety of drugs.

Until now, the use of off-label drugs in Indonesia is still being applied so that off-label drug prescribing cannot be categorized as a prescription that violates the law. Because the use of off-label drugs may benefit the patient more when there are no other options for therapy. However, prescribing off-label drugs still carries a high risk because data on adverse drug reactions (ESOs) are likely to emerge.

4 CONCLUSIONS

Based on the research that has been done, the following conclusions are obtained:

Off-label prescriptions for pediatric patients at the Saras Sehat Pharmacy, Tegal Regency are still quite high, with 48.10% off-label prescriptions and 51.9% on-label prescriptions. The prevalence of off-label categories for age (12.43%), off-label indications (1.46%), off-label contraindications (0.80%) and off-label doses (0.11%). No category of Off-Label route of administration was found. The most widely prescribed Off-Label drugs are decongestant drugs, namely Triprolidine and Pseudoephedrine.

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Regularity of antenatal care based on mother's education, pregnancy status, and gravida status

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ABSTRACT: Antenatal care (ANC) is crucial in reducing maternal morbidity and mortality. ANC is a screening process for possible risk pregnancies, so pregnant mothers with risk factors could be treated quickly. However, low utilization of health services can cut off the importance of prenatal care that should be carried out ongoing not to harm the mother and her baby. This study was conducted to identify the effect of maternal education, pregnancy, and gravida status on the regularity of ANC. This research was a quantitative study with a cross-sectional design. The population in this study were pregnant women in Dukuhwaru Public Health Center, Tegal Regency and the sampling technique was purposive sampling—data analysis using chi-square. The results showed that 39.6% of respondents are primary graduate, 11.3% has unplanned pregnancies, and 58.5% have multigravida. There was no significant relationship between maternal education and the regularity of ANC ($\rho = 0.36$), but there is a significant relationship between pregnancy ($\rho = 0.02$) and gravida status ($\rho = 0.04$) with the regularity of ANC. There is a need for health education related to the importance of family planning for those going to get married.

1 INTRODUCTION

Globally it is estimated that out of 210 million women who become pregnant. Eight million of them experience life-threatening complications every year. Every minute some women die due to complications of pregnancy and childbirth, which means that 1,400 women die every day. In addition, out of half a million women who die from complications of pregnancy and childbirth every year, 99% of them occur in developing countries such as sub-Saharan Africa and Asia. In developing countries, the risk of death is 200 times higher than in developed countries. The cause of death in developing countries is the lack of services and the lack of utilization of existing health facilities (Othman *et al.* 2017).

Globally, maternal mortality should be reduced to 70 per 100 thousand live births in 2030. The maternal mortality rate in Indonesia in 2017 was 117/100,000 live births (Susiana 2019). Tegal Regency, there were 12 cases of maternal mortality in 2019 and increased to 28 cases in 2020. Tegal Regency itself was in the third-highest MMR in Central Java (Dinas Kesehatan Provinsi Jawa Tengah 2019, 2020).

Indonesia has implemented various efforts to accelerate the reduction of maternal mortality. One of them is by providing guarantees that every mother can access quality health services such as childbirth (Kementerian Kesehatan RI 2021). Antenatal care (ANC) is crucial to directly reduce maternal morbidity and mortality. ANC is considered a screening process for possible risk pregnancies so that mothers with high-risk pregnancies are treated quickly, but low utilization of health services can cut off the importance of prenatal care that should be carried out on an ongoing basis so that it does not harm both the mother and her baby (Hijazi *et al.* 2018).

Globally, in 2006–2014, only 64% of pregnant women had routine ANC check-ups following WHO recommendation (WHO 2016). While in 2017, there were 87.065% pregnant women who received prenatal care. In the same year, ANC in Indonesia was 97.5%. Compared to Thailand, in 2016 had reached 98.1%, and China, in 2018, had reached 100% 2018 (Dinas Kesehatan Provinsi Jawa Tengah 2019; The World Bank n.d.). Factors such as mother’s education, residence, gestational age, gravida, parity, pregnancy status (planned/unplanned), and the number of living children influence ANC use. (Othman *et al.* 2017) In General, 4ANC achievement in Indonesia has decreased from 88.5% in 2019 to 84.6% in 2020. This phenomenon was also found in Central Java from 95.7% in 2019 to 94.1% in 2020 and Tegal Regency from 100% in 2019 to 94% in 2020 (Dinas Kesehatan Provinsi Jawa Tengah 2020).

In the Philippines, pregnant women living in rural areas are more likely to have regular ANC, while pregnant women in Indonesia who live in urban areas are more likely to have regular ANC (Wulandari *et al.* 2021). Previous studies have mainly referred to ANC based on 4ANC achievements (Dada *et al.* 2021; Mumtaz *et al.* 2019; Woyessa 2019), even though early detection needs to be routinely carried out, so it is necessary to study the regularity of monthly visits by pregnant women based on factors that influence the ANC. This study aimed to determine the effect of maternal education, pregnancy status, and gravida status on the regularity of ANC.

2 METHODS

This study was a quantitative study with an observational research design using a cross-sectional by measuring or observing at the same time. The population in this study were all pregnant women in the Dukuhwaru Public Health Center, Tegal Regency. The sampling technique used was purposive sampling. The inclusion criteria in this study were pregnant women in the first, second, and third trimester who had an ANC before, had an ANC at the Dukuhwaru Public Health Center, and were members of the WhatsApp group created by the Dukuhwaru Public Health Center. In contrast, the exclusion criteria were pregnant women who had never done ANC at all, pregnant women at Dukuhwaru Public Health Center who did ANC only in other places and have never been to Dukuhwaru Public Health Center, pregnant women who were not included in the WhatsApp group. The number of samples was 53 people. The independent variables in this study consisted of maternal education, the status of pregnancy, and gravida status, while ANC was the dependent variable. Pregnant women who carry out routine checks every month were categorized as having regular check-ups. This study used primary data. The data collection was carried out by filling out a questionnaire on google form in connection with implementing restrictions on community activities (Instruksi Menteri Dalam Negeri Nomor 15 Tahun 2021). Filling out the questionnaire was carried out on July 2021. The flow of study implementation is as follows (Figure 1):



Figure 1. The flow of study implementation.

We shared the google form link through the WhatsApp group formed by the midwife at the Dukuhwaru Public Health Center to communicate with pregnant women. The collected data was analyzed using Chi-Square.

The results showed that most mothers (39.6%) have a primary education background. Primary education is a basic education taken from elementary school to junior high school. The respondents’ current pregnancies are 88.7% planned pregnancies, but 11.3% of mothers have unplanned pregnancies. 58.5% of respondents are at their second pregnancy or more, known as multigravida (Table 1).

Table 1. Characteristics of respondents.

Variables	F	%
Mother's Education		
Primary Education	21	39.60%
Secondary Education	16	30.20%
Higher Education	16	30.20%
Pregnancy Status		
Unplanned pregnancies	6	11.30%
Planned pregnancies	47	88.70%
Gravida Status		
Primigravida	22	41.50%
Multigravida	31	58.50%

The relationship test on mother education obtained a ρ -value of 0.36, which means that there is no significant relationship between mothers who have primary education or higher education with the regularity of ANC (Table 2). Most mothers with higher education and primary education carried out regular ANC. A previous study stated that the education level of pregnant women had no significant effect on adherence to ANC. It is possible because other factors influence mothers, such as cultural factors, family economic status, husband's education, and family support (Mantao *et al.* 2018).

Table 2. Regularity of antenatal care based on mother's education, pregnancy status, and gravida status.

Variables	ANC		General	ρ -value
	Irregular	Regular		
Mother's Education				
Primary Education	5 (23.8%)	16 (76.2%)	21 (100%)	0.36
Secondary Education	3 (18.7%)	13 (81.3%)	16 (100%)	
Higher Education	1 (6.3%)	15 (93.7%)	16 (100%)	
Pregnancy Status				
Unplanned pregnancies	3 (50%)	3 (50%)	6 (100%)	0.02
Planned pregnancies	6 (12.8%)	41 (87.2%)	47 (100%)	
Gravida Status				
Primigravida	1 (4.5%)	21 (95.5%)	22 (100%)	0.04
Multigravida	8 (25.8%)	23 (74.2%)	31 (100%)	

When viewed in more detail, Mother's education shows that respondents with elementary education are nine people, junior high school is 12 people, high school is 16 people, and advanced education after high school is as many as 16 people. The existence of regulations related to compulsory education in Indonesia is another factor that affects mothers' knowledge (Presiden Republik Indonesia 2008). This improvement in education impacts increasing the knowledge of pregnant women about the importance of regular prenatal check-ups, and those who already have good knowledge about the importance of regular ANC participate in sharing information. Furthermore, the experience of women with primary education through friendship circles and pregnancy classes impacted that are followed (Baroroh *et al.* 2017). At the time, the midwife's ANC also provided health education (Alehegn *et al.* 2021), so this impacted the absence of influence of maternal education with ANC care regularity. The results of this study are in line with research at the Balla Health Center, Mamasa Regency, which stated that there was no relationship between maternal education and ANC (Obstetrics *et al.* 2021).

A study conducted in Ethiopia found that women who had primary education tended not to carry out ANC and tended to be late for ANC (Woldeamanuel & Belachew 2021). Similar findings at Dayanand Medical College and Hospital, Ludhiana, Punjab, India, where mothers with low education were associated with lower ANC utilization (Chopra *et al.* 2018). This is because women with higher education have broad access to information, can make their own decisions regarding health, can change views regarding the importance of carrying out routine and timely ANC. Education for women is considered important to achieve sustainable development goals related to maternal and child health. Furthermore, it can reduce infant mortality by implementing effective maternal health services (Chopra *et al.* 2018, Woldeamanuel & Belachew 2021).

Pregnancy status on the regularity of ANC in this study obtained a value of $\rho = 0.02$ which means there is a significant relationship between pregnancy status and ANC regularity. 87.2% of respondents with planned pregnancies had regular ANC, while 50% of mothers with unplanned pregnancies did not. A study conducted in South Africa also found that more women carried out regular and timely pregnancy checks with planned pregnancies than women with unplanned pregnancies (Jinga *et al.* 2019). In a planned pregnancy, the mother-to-be tends to be happy with her pregnancy, so she is more motivated to have regular and timely ANC, while in an unwanted pregnancy, the mother may find out her pregnancy too late, could not accept her pregnancy, and not ready for another pregnancy. So that there is a tendency to delay, be reluctant to carry out a pregnancy test, even to the point of neglecting the pregnancy (Haddrill *et al.* 2014). This finding was also found in Southern Ethiopia, where 69% of mothers with unplanned pregnancies were reluctant to have ANC and were four times more likely to experience late ANC (Abame *et al.* 2019).

A study in the district of Tanzania showed that nearly half of the women there had an unplanned pregnancy two years after the previous pregnancy. Delays and irregularities in ANC occurred in women with unplanned pregnancies, and the cases were higher in the second and third trimesters. Lack of family support for pregnant women without planning is suspected to be a contributing factor, so there is a possibility of being late in recognizing the risks or danger signs that pregnant women may experience (Exavery *et al.* 2013).

The p-value of the gravida status of the respondents in this study was 0.04 which means there is a significant relationship between gravida status and the regularity of ANC. Most respondents with primigravida in this study had regular ANC but not multigravida mothers. A previous study in Bhutan found a relationship between gravida status and ANC. In multigravida, mothers are more likely to be late and not routinely carry out ANC. Pregnant women with multigravida tended to feel more experienced, so they were reluctant to perform ANC. Lack of support from family and environment was another factor influencing mothers' making ANC visits (Dorji *et al.* 2019). The same finding in South Africa also stated that 85.4% more primigravida mothers had routine ANC (Abame *et al.* 2019). Primiparous mothers tend to be more interested in having a pregnancy check-up because it is their first time getting pregnant and want to monitor their pregnancy's progress optimally. Limitations in this study using a relatively small sample and only carried out in one Public Health Center in Tegal Regency. In addition, the factors studied only include maternal factors, even though many other factors influence.

3 CONCLUSION

Most respondents have a primary education background, planned pregnancy status, and multigravida. The regularity of antenatal care in this study was influenced by pregnancy and gravida. There is no relationship between the regularity of antenatal care with maternal education. Implication for midwifery practice is that midwives need to prepare teenage mothers by giving premarital counseling and family planning. Implication for further study needs to examine other factors that affect the regularity of ANC with a broader number of samples.

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Study qualitative mother knowledge and perceptions about the use of mushroom broth as a substitute of MSG

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ABSTRACT: Monosodium glutamate has developed into one of the most popular food additives in the world. When added to food, MSG gives food its delicious taste. However, consuming too much MSG is also not good for health. For example, it can increase heart rate and suffer from headaches and can cause hyperactivity and attention deficit disorders in children. One way to replace artificial flavoring is to use local plants as natural flavoring agents. The use of mushrooms as an alternative to natural seasonings in addition to providing a savory and delicious taste in cooking also provides various health benefits so that mushrooms are often referred to as functional foods. The purpose of this study was to identify the knowledge and perceptions of mothers about mushroom broth as a substitute for MSG as the first step in optimizing child growth and development. The method that will be used in this research is qualitative with phenomenological design, Data collection was conducted with in-depth interviews from respondents to determine Maternal Knowledge and Perception About the use of Mushroom Broth as a Substitute for MSG. The sample of this study was 4 mothers who had children and cooked almost every day, sampling using purposive sampling techniques, our findings showed that respondents did not know much information about mushroom broth instead of MSG. Respondents knew the health hazards of using too much MSG, but respondents still used MSG in every dish. Respondents thought that mushroom broth was not as good as MSG. Advice for respondents to improve health-related knowledge.

1 INTRODUCTION

Monosodium Glutamate or commonly known as MSG has long been used to flavor food and strengthen flavors. Usually, this MSG is added to chicken or beef broth powder which is very practical to use. Not surprisingly, many housewives consider this MSG ingredient as an effective and efficient way to enrich the taste of a dish. However, consuming too much MSG is also not good for health. Because MSG has a harmful impact on the body. For example, it can increase heart rate and suffer from headaches (Salsabila 2018).

Lifestyle in the form of consumption patterns of foods containing MSG affects the risk of attention deficit disorder and hyperactivity in children (Chikmah 2020). Consumption of artificial flavoring in large quantities for a long time will have a bad effect on body health. Effects that can occur include brain damage, damage to neurons, trigger cancer, slow the development of children's intelligence, and are not good for the health of the fetus (Sabri *et al.* 2006). Thus, it is necessary to develop alternative flavorings obtained from nature in order to reduce the use of MSG (Haq 2015). One way to replace artificial flavoring is to use local plants as natural flavoring agents (Juita *et al.* 2015).

Mushrooms have a special taste, produce a delicious and savory taste in food so they are in great demand. The type of amino acid that is glutamic acid found in mushrooms is a substance that causes the same taste as that found in meat. Glutamic acid is used as a

neurotransmitter in the brain and neurons. The glutamic acid content in mushrooms will be higher when the mushrooms are fully mature and ready to be harvested (Mouritsen 2012).

The use of mushrooms as an alternative to natural seasonings in addition to providing a savory and delicious taste in cooking also provides various health benefits so that mushrooms are often referred to as functional foods. Mushrooms contain low sodium and high potassium so they can maintain stable blood pressure. Mushrooms also help prevent chronic disease, diabetes and reduce weight because they contain no cholesterol, are low in calories, contain antioxidants, and dietary fiber such as chitin and betaglucans. Mushrooms are also very useful for a vegetarian diet because mushrooms contain high protein compounds in the form of essential amino acids which are indispensable for human health. In addition to these benefits, mushrooms are plants that contain high vitamin B complex and are the only non-animal food ingredients with vitamin D content that are used for bone health (Widyastuti *et al.* 2015).

According To Paramitha Research, Vania on the Manufacture Of Natural Flavoring Powder From Oyster Mushroom Broth As a result of research shows that maltodextrin and drying temperature quite affect the quality of oyster mushroom broth powder produced. The flavoring of oyster mushroom broth is best produced at a maltodextrin concentration of 15% and a drying temperature of 80°C, with a water content of 10.36%, an ash content of 1.22% corresponding to SNI, as well as a protein content of 9.67%, a yield of 20.05%, and a solubility value of 95.10%. The flavoring of the resulting oyster mushroom broth has a taste, smell, and color favored by panelists and has been in accordance with the SNI.

This study aims to find out Mother's Knowledge and Perception About Using Mushroom Broth in Lieu of MSG Efforts to Optimize Child Growth and Development and the benefits of this study to increase maternal knowledge about mushroom broth in lieu of MSG.

2 METHODS

The research method used is a qualitative research method with phenomenological design, the type of data used is primary data and to obtain the depth of data through the collection of the deepest data from respondents to find out how the mother's knowledge and perception of the use of mushroom broth instead of MSG is the first step in optimizing the growth and development of children. The respondents in the study were mothers who had children and cooked almost every day. Research tools use interview guidelines. The respondents in the study were 4 main informants, namely mothers who had children and cooked almost every day. Sampling is a purposive sampling technique. The study was conducted in November 2021.

3 RESULTS AND DISCUSSION

3.1 *Mother's knowledge of mushroom broth as a substitute for MSG efforts to optimize children's growth*

3.1.1 *The use of MSG and its purpose*

The results of interviews with 4 mothers said that each cook should be given MSG so that it adds to the delicacy of the food, so that the food becomes delicious and savory. 4 mothers also always use MSG in every dish. This is based on in-depth interviews with 4 mothers.

I give a little MSG when cooking, it's better to give MSG so it's delicious, the food is better (IU 1).

Not every cooking is given MSG, so there is taste. Not using micin or other brands but using Royco (IU 2).

Just use Royco, just to add flavor (IU 3).

Every cooking is given MSG, so the food is delicious (IU 4).

The results of interviews from 4 respondents showed that every time they cooked they were given MSG, although with a different brand, but the contents of the flavoring

contained MSG. Respondents added MSG to their food with the aim of making it delicious, flavourful, savory and adding a good taste to the dish.

The results of the study I Nyoman Adiyasa. Maternal Knowledge Level, Role of Health And Behavioral Officers Use Of Flavoring Monosodium Glutamate (Msg) In Cooking From the results of the study is still largely knowledgeable less with the use of flavoring monosodium glutamate (MSG) and health workers do not play a role, but the behavior of use is still classified as safe.

Monosodium L-glutamate (MSG) and 5'-ribonucleotides such as disodium 5'-inosinate (IMP) and disodium 5'-guanylate (GMP) are the source of the umami taste (as the fifth basic taste) found in food and act on soy receptor cell membranes as well as sugar, salt, vinegar and coffee. These flavors are present in a wide variety of foods and have an important role in enhancing taste and taste. For example, in Japanese broth known as dashi and some fish sauce from Southeast Asia. With small amounts, the addition of MSG, IMP and GMP can strengthen the umami (savory) taste in dishes (Kurtanty *et al.* 2018).

3.1.2 *The effects of consuming too much MSG for health and child's growth and development*

Respondents do not know the dangers that can be caused by excessive consumption of MSG. Respondents only know that it is dangerous if given in excess, but they do not know what dangers are caused, especially the dangers caused by giving to children.

It seems that MSG is not good for health, I heard that it can cause disease, but I don't know what disease. MSG is not good for children, but I don't know the info (IU 1).

MSG is not good for health can cause coughing, sore throat. Can interfere with growth and development of children often sick (IU 2).

If you have too much MSG, something can happen, it's not good for the brain, I don't know that MSG can interfere with children's growth and development (IU3).

Not good for health, can make tonsils. It can interfere with a child's growth and development if it is excessive, what tissue damage can be done ... organs (IU4).

Monosodium has been shown to be toxic to humans and experimental animals. The side effects reported by various studies can be summarized as the appearance of metabolic/digestive, respiratory, circulatory, and nervous system anomalies. It was found that MSG exposure of mice in the neonatal stage can severely damage their hypothalamic nuclei (arcuate nucleus and ventromedial nucleus), resulting in increased body weight, fat deposition, decreased motor activity, and growth hormone secretion (Tawfik & Al-Badr 2012). Lifestyle in the form of consumption patterns of foods containing MSG affects the risk of attention deficit disorder and hyperactivity in children.

3.1.3 *Mushroom broth instead of MSG*

Based on the results of in-depth interviews, it was found that MSG can be replaced with salt or sugar.

MSG can be replaced with sugar (IU 1).

Never used a substitute for MSG, namely mushroom broth (IU 2).

Sometimes parents use sugar, give it a little sugar if it's for small children, they say that (IU 3).

If you don't use MSG, just use salt (IU 4).

There is only 1 respondent who knows that mushroom broth can be used as a substitute for MSG. Based on Wang's research (2019) which aims to compare the effect of MSG and its alternatives on the taste characteristics of chicken soup, it was found that mushroom extract had an umami flavor concentration equivalent to MSG (Wang *et al.* 2019).

3.1.4 Information about mushroom broth

Researchers dig deeper into the mother's knowledge about mushroom broth that can be used as an alternative to MSG.

I don't know, I don't know any information about mushroom broth and I've never used it either (UI 1).

Yes, I got info on mushroom broth as a substitute for MSG from Facebook. Never used and for my children's cooking. I don't know the content of mushroom broth (UI 2).

I've never heard of mushroom broth, I've tried it from a relative's dish, but I just tried it a little ... (UI 3).

I have ever received information that mushroom broth can be a substitute for MSG from Facebook, Instagram. I don't know what mushroom broth is made of ... (UI 4).

Respondents' knowledge about mushroom broth as a substitute for MSG is still lacking because mothers have never received proper information from experts. As for respondents who know about information from mushroom broth, information obtained from social media.

Sensing occurs through the five human senses, namely: the senses of sight, hearing, smell, taste and touch. Most of human knowledge is obtained through eyes and ears. Knowledge is a very important domain for the formation of one's actions. Behavior that is based on knowledge and awareness will be more lasting than behavior that is not based on knowledge. The umami taste is a type of taste attribute that is very different from the traditional four flavors. This addition of umami substances such as mushrooms will change the taste characteristics of the food. Not only the umami taste but also other sensory characteristics such as continuity, full mouth, impact, softness, and thickness will increase. Overall, they improve the palatability of foods. The EUC values of the commercially available mushroom fruiting bodies and mycelia summarized here are of great value for their further use as food or food flavoring agents and in health food formulations (Leun Mau 2005).

3.2 Mother's perception of mushroom broth as a substitute for MSG

Based on the results of in-depth interviews with 4 respondents, various perceptions regarding mushroom broth were obtained. They think that MSG is tastier than mushroom broth, but the benefits of mushroom broth are better than MSG.

I've never used mushroom broth and don't know the info, but it's not good to cook if you don't use MSG (UI 1).

Have you ever heard of mushroom broth from Facebook, that's why now if you cook for children using mushroom broth, it's better for health than MSG (UI 2).

I don't like using mushroom broth, I like using Royco (UI 3).

Mushroom broth is good for health, I know from Facebook and Instagram but I don't know the taste yet ... (UI 4).

Perception is a process that is preceded by sensing, namely the process of receiving a stimulus by the individual through the senses or can be called a sensory process. However, the process does not just stop, but the stimulus is continued, and the next process is called the perception process. The process includes sensing after the information is received by the senses, the information is processed and interpreted into a perfect perception (Walgio 2005).

Respondents have never received proper information from experts regarding mushroom broth, so the perceptions obtained from respondents come from their experiences. Respondents already know that MSG if consumed in excess will cause health problems, but respondents still use MSG in every dish.

Besides having a savory taste, mushrooms also have many benefits for the body. For example, in shitake mushrooms, can prevent cancer because it contains lentinan. In straw mushrooms, good for diabetics because it contains natural insulin. The benefits of button mushrooms are to increase the number of red blood cells because button mushrooms contain folic acid, also known

as vitamin B (Tawfik & Al-Badr 2012). The use of natural flavoring ingredients from mushrooms has been discovered by graduates of the Teacher Training and Education Institute PGRI Jember using oyster mushrooms and has been produced in large quantities (Paramitha 2020).

Mushrooms contain low sodium and high potassium so they can maintain stable blood pressure. Mushrooms also help prevent chronic disease, diabetes and reduce weight because they contain no cholesterol, are low in calories, contain antioxidants, and dietary fiber such as chitin and betaglycans. Mushrooms are also very useful for a vegetarian diet because mushrooms contain high protein compounds in the form of essential amino acids which are indispensable for human health. In addition to these benefits, mushrooms are plants that contain high vitamin B complex and are the only non-animal food ingredients with vitamin D content that are used for bone health (Widyastuti *et al.* 2015).

4 CONCLUSION

Respondents do not know much information about mushroom broth can be a substitute for MSG. Respondents know the health hazards of using too much MSG, but respondents still use MSG in every dish. Respondents thought that mushroom broth was not as good as MSG. advice for further research to further increase public interest in health.

ACKNOWLEDGMENTS

Thank you to Polytechnic Harapan Bersama for supporting this research. Thanks, were also conveyed to the respondent (Group of Women Farmers Jakwire Tegal).

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Stunting on the development of children aged 2–6 years in East Tegal district, Tegal city

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ABSTRACT: Malnutrition in children can cause a child to experience various growth and development disorders, such as wasting and stunting. Stunting experienced by children can be caused by not being exposed to the 1000 HPK period or the First Day of Life with special attention that determines the level of intelligence of children, physical growth of children, and a person's productivity in the future. Motoric movements in children cannot be carried out properly if the level of muscle maturity has not yet been developed. In stunted children, the mechanical ability of the striped muscles is low, because the slow level of muscle maturity causes motor skills in children to be hampered. This research is a quantitative study that aims to determine the effects of stunting on the development of children aged 2–6 years, with a cross sectional study design. The research was conducted in Panggung Village, Tegal Timur District, Tegal City, the number of respondents was 30 children. Primary data was the result of measuring TB and child growth and development. Data analysis used the chi square test. The results showed that stunting could affect the development of children aged 2–6 months where the test results showed a p-value of 0.02. Suggestions for further research using a larger number of respondents.

1 INTRODUCTION

Lack of nutrition in children can cause a child to experience various growth disorders, such as *wasting* and *stunting*. Stunting is a condition when a toddler has a length or height that is less than his age. The diagnosis is determined by looking at the results of measurements of length or height with results of more than minus two standard deviations of the WHO child growth standard median. Stunting is a chronic nutritional problem with several causative factors including nutritional conditions during pregnancy, socio-economic conditions, morbidity in infants, and lack of nutritional intake during infancy. In the future, a child with stunting may experience difficulties in achieving optimal physical and cognitive development (Kementerian Kesehatan RI 2018).

Stunting is a condition in which children fail to thrive at the age of less than five years due to chronic malnutrition, causing children to be too short for their age. Malnutrition generally occurs when the child is still in the mother's womb or in the early stages of the baby's birth, however, stunting usually occurs after the baby is approximately 2 years old (Tim Nasional Percepatan Penanggulangan 2017).

Conditions of chronic malnutrition will cause stunting (height for age less than 2 SD based on the normalization of Z values in children of the same age and sex) and in several studies it has been stated that there is a relationship between stunting/stunting and delayed child development (Miller *et al.* 2015).

Malnutrition in children will have an impact on increasing the risk of death caused by communicable diseases, delays in cognitive development in childhood, poorer educational outcomes and shorter stature, and decreased outcomes or income in adulthood. For low- and middle-income countries, there is a lot of empirical literature which states that there is a relationship between linear growth and educational attainment and/or cognitive outcomes in children at school age (Ali *et al.* 2014).

Stunting experienced in childhood can be caused by a lack of attention during the 1000 HPK period or the First Day of Life so that it affects one's intelligence, physical growth rate, and productivity in the future. Besides that, the cause of stunting can also be due to a lack of attention from parents during the golden age, which starts from 1000 HPK, namely the formation of child growth and development. At that time, the nutrition that the baby received while in the womb and was exclusively breastfed had an impact on the long term of the child's life while growing up. If this can be exceeded properly, it will avoid stunting in toddlers and poor nutritional status (Fikriyati 2015).

Stunting can be said as a condition of children who experience chronic malnutrition which can be related to the development of the child's brain. Caused by a delay in the maturation of nerve cells in the motor coordination center, which is located in the cerebellum (small brain). The delay in maturation of nerve cells is influenced by the number of *cortical dendrites*, *myelin* in the *spinal cord*, and reduction of *neurotransmitter synapses*. In addition, *stunting* has a relationship with low maturity of muscle function which causes a decrease in the mechanical ability of the triceps muscle, thereby causing disruption of children's motor development (Solihin *et al.* 2013). Motor movements in children cannot be done properly if the level of muscle maturity has not developed. In children who experience stunting, the mechanical ability of *striped muscle* is low, because the level of muscle maturity is slow, causing motor skills in children to be hampered. This delay can be influenced by various factors, namely heredity, environment, child's personality, muscle disorders, and obesity (Pantaleon *et al.* 2015).

Motor development of children is divided into two, namely fine motor and gross motor. Fine motor skills are smooth movements that occur by involving certain parts that are carried out with small muscles, because they do not require a lot of energy but require careful coordination (Pantaleon *et al.* 2015). Included in the fine motor skills are doodling on paper, arranging blocks, drawing straight lines, drawing circles, choosing a longer line drawing, and drawing a plus sign according to age. Then, gross motor skills are defined as body movements in moving the muscles in part or all of the limbs that can be influenced by the maturity of the child himself (Fikriyati 2015).

Research that was conducted in Sleman Yogyakarta Regency on children aged 12–60 months with a sample of 106 children found that there was a significant relationship between stunting and children's motor development with the test results getting an OR value of 3.9 which means between the development of the suspected child. It is possible that children with stunting conditions have a risk of 3.9 times greater than children who have normal development (Robosiwi *et al.* 2017).

Another study conducted in the Aceh region on kindergarten children aged 3–5 years showed that there was a relationship between stunting and gross motor development. It was found that children who experienced gross motor development delays were more common in children who were stunted by 73% compared to children who were not stunted by 30.6% (Hudaini 2011). Another study also conducted in the North Coast region of Cirebon City also had similar results, namely there was a significant relationship between stunting and fine motor skills (p value <0.01) and there was a relationship between stunting and gross motor skills (p value <0.01). The study was conducted on 166 children aged 12–60 months (Hizni *et al.* 2010).

Abnormal developmental delays in children can be characterized by slow maturation of nerve cells, social responses, motor movements, and lack of intelligence in children (Yuliana 2004). In recent years, there has been an increase in the incidence of child delays in terms of motor skills, language, behavior, and autism in the United States 12–16%, Argentina 22%, Thailand 24%, and Indonesia 13–18%. Based on the results of a survey conducted in 2006, it

is known that at least 16% of toddlers or toddlers in Indonesia experience delays in nerve and brain development ranging from severe to mild (Fikriyanti 2015).

Nursadiyah stated that the results of the study found that 2 out of 1,000 babies born experienced delays in motor development. The condition of stunting that occurs in toddlers is a nutritional problem that is experienced by many toddlers in the world today. In 2017 there were 22.2% or around 150.8 million children under five in the world experiencing stunting. In 2017 it was also found that more than half of stunted toddlers were toddlers from Asia (55%), while more than a third of stunted toddlers (39%) were toddlers from Africa. The number of stunted children under five in Asia is 83.86 million, and the highest proportion comes from South Asia (58.7%) and the lowest proportion is from Central Asia (0.9%).

Based on the results of Nutrition Status Monitoring (PSG) data show that in the last three years, short or short toddlers have a higher prevalence than other nutritional problems, which include undernutrition, wasting, and obesity. The prevalence of short toddlers or stunting has increased from 27.5% in 2016 to 29.6% in 2017 (Kementrian Kesehatan 2018).

The prevalence of stunting in Indonesia is still high. Based on the 2018 Basic Health Research (Riskesdas), the prevalence of stunting in Indonesia in 2018 was 30.8%, this figure is still very far from the WHO target of a maximum of 14%. The prevalence of stunting in Central Java is still quite high at 31.22%. Tegal City is one of the cities in Central Java which still has a high number of stunted children under five, namely 830 children aged 0–5 years (Kementrian Kesehatan 2018).

The novelty raised in this study is that there are many theories which state that stunting will affect the process of growth and development of toddlers, this may also affect toddlers who are in the Tegal Timur Village area. The purpose of this study was to determine whether there is an effect of stunting on the development of children aged 2–6 years.

2 METHODS

This research is a quantitative research with a cross-sectional research design, the population in this study is children aged 2–6 years who experience stunting in the Panggung Village, East Tegal District, Tegal City. The sample was used using a total sampling technique of 30 respondents consisting of 15 children who were stunted and 15 normal children. Primary data collection was carried out by recording toddlers and measuring toddler development, both for toddlers who were stunted and toddlers who were not stunted or normal. Data analysis using chi-square test.

3 RESULT AND DISCUSSION

The results of the measurement of nutritional status are shown in Table 1, namely 50% of respondents are stunted and 50% are normal, most of the respondents are not working as much as 19 respondents (63.3%), most of the respondents have secondary education, namely 26 respondents (86.7%), most of the respondents have abnormal development, namely 20 respondents (66.7%).

Table 1. Frequency distribution of respondents.

	f(%)
Toddler Nutritional Status	15 (50%)
Stunting	
Normal	15 (50%)
Mother's Job	
Work	11 (26.7%)
Does not work	19 (63.3%)

(continued)

Table 1. Continued

	f(%)
Mother's Education	
Base	4 (13.3%)
Intermediate	26 (86.7%)
Child development	
Normal	10 (33.3%)
Abnormal	20 (66.7%)
Total	100 (%)

3.1 Description

The p value was obtained by using the *Chi Square* test analysis.

*Meaningful difference if $p < 0.05$, **very significant if $p < 0.01$

Based on the results presented in Table 2, it can be seen that there is an influence between stunting and the development of children aged 2–6 months as seen from the test results with a p value of 0.02.

Table 2. The effect of stunting on child development.

Nutritional status	Development		Total	p Nilai value
	Normal	Abnormal		
Stunting	2 (13.3%)	13 (86.7%)	15 (50%)	0.02
Normal	8 (53.3%)	7 (34.8%)	15 (50%)	
Total	10 (33.3%)	20 (66.7%)	30 (100%)	

Indicators of well-being in childhood and a reflection of social welfare can be seen from cases of stunting. The incidence of stunting or lack of nutritional status of children in 2013 was recorded as many as 161 million children worldwide where the average condition was below -2 SD based on body length for age/height for age. Impaired growth and development usually does not occur immediately but often begins when the child is still in the womb and continues for at least the first 2 years of a child's life. The presence of failure in child growth is closely related to pathological disorders, namely an increase in morbidity and mortality, loss of potential for physical growth, decreased neurodevelopment and cognitive function, increased risk of chronic disease in adulthood. Severe physical damage and neurocognitive disorders where this growth disorder is a major threat to human development. Awareness of reducing stunting and its consequences is a top global health priority and focuses international attention at the highest level with global targets set for 2025. The challenge that must be faced is preventing linear growth failure and protecting children from overweight and obesity (de Onis & Branca 2016).

Attention to the importance of adequate nutrition during pregnancy and infancy is very important, especially in developing countries, because the impact of early nutritional deficiencies affects long-term brain function, cognition, and productivity. Although many other factors contribute to permanent cognitive deficits in humans, they include interaction with the environment, the timing and extent of nutritional deficiencies, and the possibility of recovery. These factors should also be considered in the design and interpretation of future research. Several types of malnutrition will clearly interfere with brain development, including severe acute malnutrition, chronic malnutrition, iron deficiency, and iodine deficiency. One proven strategy is consuming iodized salt and micronutrient powders which have been shown to improve malnutrition, although direct evidence of their impact on brain development is scarce. Other These strategies also require

further research, including iron and other micronutrient supplements, essential fatty acids, and fortified food supplements during pregnancy and infancy (Prado & Dewey 2014).

Data from the 2016–2017 survey results from Nigeria were used to determine the relationship between a child's height, length of mother's education, and developmental indicators. The approaches are conventional approaches in which control variables are selected on an ad-hoc basis, and multiple machine learning (DML) approaches which use data-driven methods to select controls from a much wider set of variables and thereby reduce the potential for variable bias to be eliminated. Overall, the analysis confirms that maternal education and the incidence of chronic malnutrition have a significant direct effect on measures of early childhood development. Point estimates based on ad-hoc specifications tend to be larger in absolute values than those based on DML specifications. In rural areas, maternal education affects early childhood development both directly and indirectly through its impact on the nutritional status of older and younger children. In contrast, in urban areas, where the average level of maternal education is much higher, an increase in maternal education only has a direct effect on children's PAUD measures. Still, it does not have indirect effects on child nutrition. Thus, DML provides a practical and feasible approach to reduce threats to internal validity for strong conclusions and policy design based on observation data (Skoufias *et al.* 2021).

This study is in line with research conducted by Alam *et al.* which stated that stunting at an early age and higher TFR concentrations were associated with lower cognitive development scores at the age of 5. Socioeconomic status also has a positive relationship with cognitive development in children aged 5 years. This shows the importance of potential programs to address persistent stunting and iron deficiency in the early years of life. Initiatives that must be taken to tackle stunting early include increasing birth weight, socioeconomic status, and clean water treatment practices (Alam *et al.* 2020).

The results of this study are in line with those stated by Prado and Dewey who say that malnutrition affects physical growth, physical activity, and motor, cognitive, and social-emotional development. Malnutrition affects brain development in two ways. The first path is through caregiver behavior and the second is through the child's interaction with the environment (Prado & Dewey 2014).

Research conducted in the South Asian region, showed that stunting and being underweight affected learning achievement in children aged 36–59 months. And there is no influence between nutritional status and social-emotional development. These associations vary by domain and country. These results are based on emerging evidence that interventions that increase linear growth and reduce stunting may have a positive impact on developmental outcomes in infancy and early childhood. The integration of nutrition interventions and strategies to increase stimulation and early learning are likely to have a synergistic positive impact on early childhood development and should be a priority investment in the South Asian region (Kang *et al.* 2014).

The results of this study are in line with research conducted in Sleman Regency, Yogyakarta in children aged 12–60 months, with a sample of 106 children showing the results that there is a significant relationship between stunting and children's motor development, namely with an OR value of 3.9 which has meaning between the development of children who suspect the possibility of children with stunting is 3.9 times greater than that of children whose development is normal (Probosiwi *et al.* 2017).

The results of a study conducted in Jamaica on adolescents aged 17 years who had a history of stunting showed that stunted children had significantly higher levels of anxiety (regression coefficient 3.03; 95% CI 0.99, 5.08), while depressive symptoms higher (0.37; 95% CI 0.01, 0.72) and lower self-confidence (21.67; 95% CI 20.38, 22.97) than children who are not stunted (Tadele *et al.* 2022). A systematic review of 68 articles concluded that each one-unit increase in the HAZ (z-score of height for age) for children <2 years was associated with an increase in cognitive scores of +0.22-SD at ages 5 to 11 years (95% CI, 0.17-0.27; I² = 0%). Improved HAZ was also significantly associated with earlier walking ability and better motor scores (Skoufias & Vinha 2021). Data from cohort studies show that by controlling for socioeconomic status, gender, and mother's education, someone who is stunted at age 2

completes school 1 year later than children who are not stunted (de Onis & Branca 2016). In another analysis, an increase of 1 SD HAZ at 2 years of age was associated with a 24% reduced risk of not completing SMA (Adair *et al.* 2013).

Stunting (length-for-age z-score < 2) before age 2 years is associated with poor child development indicators, but population-level information is scarce in South Asia, the region with the highest stunting burden. Research about relationship between z scores (ie, height for age [HAZ], weight for age [WAZ], and weight for height [WHZ]) and malnutrition (ie, stunting [HAZ < 2], underweight [WHZ < 2], and underweight [WAZ < 2]) with learning/cognitive and socio-emotional development of children aged 36–59 months. Data from the Multiple Cohort Indicators in Bangladesh (n = 8,659), Bhutan (n = 2,038), Nepal (n = 2,253), and Pakistan (Punjab n = 11,369 and Sindh n = 6,718) were used. Children are considered developmentally “on-track” in the learning/cognitive or social-emotional domains if they meet certain early childhood development criteria. Meta-analyses were performed for regional associations, adjusting for socioeconomic status, early childhood education, and quality of care. In the pooled sample, learning/cognitive development was positive with HAZ (OR = 1.17, 95% CI [1.07, 1.27]) and WAZ (OR = 1.18, 95% CI [1.07, 1.31]) and negatively associated with stunting (OR = 0.72, 95% CI [0.60, 0.86]) and wasting (OR = 0.75, 95% CI [0.66, 0.86]) but not associated with WHZ or waste. Development of the appropriate pathway socio-emotional domain was not associated with z scores or indicators of malnutrition. In several South Asian countries, stunted children tend not to be “on” the developmental pathway” for learning/cognition. It is possible that interventions that prevent stunting can benefit child development, leading to significant individual and social benefits given the large burden of stunting in regions such as South Asia (Kang *et al.* 2016).

Likewise, research conducted in Aceh on kindergarten children aged 3–5 years showed a relationship between stunting and gross motor development. It was found that children who experienced gross motor development delays were more common in children who were stunted by 73% compared to children who were not stunted by 30.6% (7). Another study conducted in the North Coast area of Cirebon City also had almost the same results, namely there was a significant relationship between stunting and fine motor skills (p-value <0.01), and there was a relationship between stunting and gross motor skills (p-value <0.01). , 01). This study was conducted on 166 children aged 12–60 months (Hizni *et al.* 2010).

This research is also in line with research conducted by Yadika (2019) who conducted research on the effect of stunting on cognitive development and learning achievement. The review is carried out by looking for appropriate references. Based on this study it was found that there was an effect of stunting on cognitive development and learning achievement. Stunted conditions can cause disturbances in the process of brain neuron maturation as well as changes in brain structure and function which can cause permanent damage to cognitive development. This condition causes children’s thinking and learning abilities to be disrupted and ultimately reduces the level of attendance and learning achievement. Thus it can be concluded that there is an effect of stunting on cognitive and intelligence development.

4 CONCLUSION

The nutritional status of the respondents is 50% stunting and 50% normal, most of the respondents have abnormal development, namely as many as 20 children (66.7%), there is an influence between stunting and the development of children aged 2–6 years with p value of 0.02.

The limitation of this study is that the study was only carried out in the village area of Stage so it cannot describe the entire stunting population in the Tegal city area. So it is hoped that future researchers can conduct research with more samples so that they can represent all the population in the Tegal City area.

ACKNOWLEDGMENTS

Thank you to Polytechnic Harapan Bersama for supporting this research. Thanks, are also conveyed to respondents in Tegal Regency who are willing to be respondents in this study.

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The effect of age, parity, and pregnancy distance on low-birth-weight babies

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ABSTRACT: The Infant Mortality Rate (IMR) is one of the health indicators included in Sustainable Development Goals (SDGs) targets for the period 2015–2030. LBW baby is a condition where babies are born weighing less than 2500 grams. It contributes 60%–80% to neonatal mortality. In Tegal regency, from January to September 2021, the number of live births was 26,916, with 1,252 LBW cases (4.7%) and the highest case was in Pangkah Subdistrict with 69 cases. This study aims to determine the effect of age, parity, and pregnancy distance on the incidence of LBW. The research was quantitative with the correlational method using a retrospective approach taking secondary data from medical records. The sample was total sampling, the entire population of LBW babies as many as 69 cases born in January–September 2021 at Puskesmas Pangkah, Tegal Regency. The independent variables included maternal age, parity, and gestational spacing and the dependent factor was LBW baby. The statistical test used multiple logistic regressions. The results showed that there was an effect of age variable (0.046), parity (0.036), and gestational distance (0.005) on LBW babies. Therefore, factors taken by the mother can influence the incidence of LBW.

1 INTRODUCTION

Low-birth-weight (LBW) baby is one of the most important determinants of perinatal survival, infant morbidity and mortality, and the risk of developmental disorders and diseases in future life (Tessema *et al.* 2021).

LBW has a serious impact on the growth and development of newborns. They had a higher risk of facing a cognitive disorder such as mental retardation. Moreover, their lungs are not fully developed which is at risk of asphyxia. The immune system is not good enough for a normal-weight baby; it is easier to get pain and even death (Hartiningrum & Fitriyah 2016).

According to WHO (2018), the prevalence of incidence of LBW in the world is 20 million (15.5%) each year and developing countries are the highest contributors (about 96.5%) (Novitasari *et al.* 2020). Indonesia is a country with a high prevalence of LBW. This is evidenced that Indonesia is the 9th in the world in terms of LBW incidence, with more than 15.5% of infants each year (Hasnidar *et al.* 2020). In Central Java 2021, the incidence of LBW is still relatively high, with 46.4% of neonatal mortality caused by LBW babies (Dinas Kesehatan Provinsi Jawa Tengah 2020).

One of the supporting factors causing the occurrence of LBW is the age of the mother-to-be at high risk. The impact of LBW on infants includes asphyxia, problems in breastfeeding, hyperbilirubinemia, and idiopathic respiratory distress syndrome that can cause infant death. Ministry of Health has carried out some ways to reduce MMR and IMR such as getting closer midwife care to the community, and providing additional authority to

Puskesmas to manage Basic Emergency Obstetric and Newborn Care (PONED) (Hartiningrum & Fitriyah 2018).

A woman's best reproductive age is between 20 and 35 years; under and over age, it can increase the risk of pregnancy and childbirth. The research result conducted by Cahyani at RSUD Dr. Soediran, Surakarta (2015) showed that the majority of maternal age who gave birth to LBW babies was <20 and >35 years. While the maternal age between 20 and 35 years had a lower case of LBW (Haryanto *et al.* 2017). This is in line with the study about factors on LBW undertaken in Iran (2015), which were low parity, maternal age, and a history of preterm delivery. The study showed that efforts or strategies in preventing LBW babies could be performed by avoiding preterm delivery, optimizing pregnancy in the healthy reproductive age, and improving the high quality of healthcare services (Momeni *et al.* 2017).

The number of live births in Tegal Regency 2021 from January to September was 26,916 with 1,252 LBW cases (4.7 %). The highest number, as many as 69 cases, is in the Pangkah sub-district (Puskesmas Pangkah 2021). This study aims to determine the effect of age, parity, and pregnancy distance on the incidence of LBW, by knowing the factors that influence the incidence of LBW, it is hoped that these factors can minimize the incidence of LBW.

2 METHODS

The study was qualitative correlational research with a retrospective approach. The population was all LBW babies who gave birth in January–September 2021 at Puskesmas Pangkah Tegal Regency, as many as 69 cases, were taken by total sampling technique. In this study, independent variables were age, parity, and pregnancy distance. The secondary data was taken from patients' medical records of mothers who gave birth at Puskesmas Pangkah. The quantitative analysis used crosstab from all variables to determine the effect of each independent and dependent variable (Sugiyono 2015). The data were analyzed with multiple logistic regression analysis.

3 RESULTS AND DISCUSSION

Based on the Table 1, most of the respondents are mothers of reproductive age (20–35 years); 48 people (70%) and 21 respondents (30%) are aged less than 20 years.

Table 1. Frequency distribution of age of mothers having LBW newborns at Puskesmas Pangkah, Tegal Regency.

No	Variable	Frequency	%
1	<20 years	21 people	30 %
2	20–35 years	48 people	70 %
TOTAL		69 people	100 %

Maternal age with high parity, under 20 and over 35 years, can experience the incidence of LBW. Too young women have poor blood flow to the uterus, which can interfere with the transport of nutrients from the mother to the fetus (Hartiningrum & Fitriyah 2016). It was in accordance with the research in Ethiopia conveying that factors of sociodemographic, maternal age, income, education, and history of consuming alcohol showed a statistical relationship on the weight of newborns. Age and income had a positive relationship with neonatal weight. On the obstetric factor, multigravida mothers had better neonatal weight

than *primi gravida* mothers. Maternal nutrients also influence the birth weight of newborns (Wubetu *et al.* 2021).

The age of a woman is the most important thing in considering planning for pregnancy because the age determines prognosis of delivery causing morbidity or complications both for the mother and the fetus. A woman's reproductive age is between 20 and 30 years and it is evident that there is a relationship between age and the incidence of LBW. The blood circulation to the cervix and uterus for adolescents is not fully developed so it can interrupt the process of transferring nutrients from the mother to the fetus. The adolescent nutrients also play a role because they need to be shared with the fetus. The incidence of LBW increases with advanced maternal age by having the changes of blood vessels and the decrease of hormonal regulation of the reproductive system (endometrium). The more the age of the pregnant woman, the lower the hormonal regulation of the reproductive system they get. One of the hormonal regulations is estrogen, a hormone secreted by the ovaries in response to hormones of the anterior pituitary gland. The decrease in hormones is also followed by the reduction of the function of hormones. The estrogen functions are to increase uterine blood flow, produce a proliferative endometrium, and facilitate the development of the endometrium gland used to assist in distributing nutrients from the mother to the fetus. Low estrogen levels and imperfect endometrial development cause a decrease in uterine blood flow and also influence the transfer of nutrients to the fetus. Another hormone is progesterone which functions to keep a pregnancy going. This hormone is produced by the formed placenta; if it is produced in low levels, it will cause preterm delivery (<37 weeks) followed by LBW. Pregnant women aged >35 years will increase the risk of disease as hypertension which is one of the factors causing LBW babies (Rochjati 2011).

Table 2. A frequency distribution of mother parity having LBW newborns at Puskesmas Pangkah, tegal regency.

No	Variable	Frequency	%
1	Primipara and Multipara	51 people	74 %
2	Grand multipara	18 people	26 %
Total		69 people	100 %

Table 2 shows that 74% of respondents are Primipara and multipara, and 26% of respondents include Grand multipara.

Generally, parity has an effect ($p = 0.036$); however, it cannot be identified which parity has a risk for LBW. Parity is the number of children born to a woman. During childbirth, the uterus will face muscle strains. The more often the women were pregnant and gave birth, the closer the pregnancy distance the childbirth. It decreased the elasticity of the uterus thus it had no complete contractions (Prawirohardjo 2014). The number of babies born to a woman is an important thing in determining maternal and infant prognosis. Childbirth primipara tends to have a high risk of mothers and babies which can decrease at the second and the third parity, rise again at the fourth parity, and so on (Rustam 1989). The result showed that there was an effect between parity and the incidence of LBW. The incidence happened to mothers with parity >4 because of the existence of scar tissue by the previous pregnancy and delivery. The scar tissue causes insufficient blood flow to the placenta, resulting in a partial placenta that is thinner and fulfills the broader uterus. Besides, the result of the attachment abnormalities placenta is inhibiting the nutrients from the mother to the fetus. The incidence of LBW in mothers with the first parity was caused by the lack of experience and knowledge of pregnant women in dealing with the pregnancy (Mahayana *et al.* 2015).

Table 3. Frequency distribution of pregnancy distance having LBW newborns at Puskesmas Pangkah, Tegal Regency.

No	Variable	Frekuensi	%
1	≤ 2 years	29 people	42 %
2	3–9 years	40 people	58 %
TOTAL		69 people	100 %

Table 3 describes that there are 58% of respondents who have a pregnancy distance of 3–9 years and 42% of respondents of <2 years.

Pregnancy distance is also significantly affected ($p = 0.005$) where a distance of ≤ 2 years has no effect with 0.9 times the risk of LBW. However, the pregnancy distance of 3–9 years has a significant effect ($p = 0.003$) with 0.0 times facing LBW. To sum up, the ideal pregnancy distance has a lower risk of having an LBW baby.

Another factor was pregnancy distance. A good pregnancy distance is > 2 to 5 years; if it is under 2 years, the mothers have a high risk for preeclampsia and other complications during pregnancy and even having an LBW baby. The research results from Colti S. at RSUD Semarang (2014) obtained that mothers with pregnancy distance of <2 years, as many as 18 respondents (78.2%), reported LBW babies. Also, 5 mothers (21.7%) with a pregnancy distance of ≥ 2 years had a baby with LBW. On the other hand, mothers with a pregnancy distance <2 years had more LBW babies (Nur *et al.* 2016).

In the female reproductive cycle, the minimum pregnancy distance to keep the organ and reproductive system going is 24 months, while the ideal pregnancy distance is between 2 and 9 years. The statistical test stated that there was an effect between pregnancy distance and LBW. Women who are pregnant with too close of a distance from the previous pregnancy can provide a worse prognosis for the health of the mother and baby. This is due to an imperfect form or function of the reproductive system. (Cunningham *et al.* 2014). The pregnant mothers with parity >2 years have 14.083 times greater in having LBW. This was in line with the study by Colti Sistiari at RSUD Banyumas (2018) stating that there was a relationship between pregnancy distance and the incidence of LBW with a p-value of 0.004. Also, the research conveyed that pregnancy distance <2 years had a 52.111 times greater chance than the mothers with a pregnancy distance ≥ 2 years. The nearest pregnancy distance can cause anemia because the mother's condition has not recovered yet and the fulfillment of nutrients is imbalanced; however, the mother must fulfill the fetus's nutrients. Pregnancy distance under 2 years influences the next pregnancy because of the unprepared mother's womb. Psychologically, the mothers are not ready yet since the baby still needs more attention. The next pregnancy should be available after having a pregnancy distance of more than 2 years (Cunningham *et al.* 2014).

Table 4. The analysis of the effect of maternal and fetal risks on LBW.

Variable	Category	p	OR	Note
Effect of age on LBW	Age	0.046		Having an effect
	1 (<20 years)	0.314	0.286	
	2 (20–35 years)	0.018	0.108	
Effect of parity on LBW	Parity	0.036		Having an effect
	1 (Primipara & Multipara)	0.598	7.167	
	2 (Grand Multipara)	0.972	0.883	
Effect of pregnancy distance on LBW	Pregnancy distance	0.005		Having an effect
	2 (≤2 years)	0.929	0.900	
	3 (3–9 years)	0.003	0.026	

Table 4 indicates that maternal age has an effect on the incidence of LBW at Puskesmas Pangkah with a significance of 0.046; age under 20 years has no significant effect and has 0.2 times the risk of experiencing LBW baby. However, healthy reproductive age (20–35 years) is significantly influenced (0.018) with 0.1 times the risk of LBW. Therefore, mothers of reproductive age have a lower risk of having LBW babies.

To decrease MMR, midwife plays a strategic role. It is because of having a capacity to facilitate maternity services, and provide maternal and child health education. The midwife can also carry out the early detection of referral cases especially in rural areas. In collaboration with doctors, midwife plays a role in improving the use of contraception as a preventive action for a woman in 4 categories; too young (<20 years), too old (>35 years), too frequent (<2 years), and too many (>2 children) (Hartiningrum & Fitriyah 2016).

The limitation of this study is that this study only discusses the effect of age, parity, and pregnancy distance on the incidence of LBW, there are still assumptions about other factors that have not been studied such as nutritional factors, environmental factors, or maternal health history.

4 CONCLUSION

Most of the respondents in this study were mothers of reproductive age (20–35 years) as many as 70%. The majority of respondents were primipara and multipara (74%) and the rest included Grand multipara. Most of the respondents had a pregnancy distance of 3–9 years (58%). The result of multiple logistic regression analysis showed that there was an effect of age, parity, and pregnancy distance on the incidence of LBW at Puskesmas Pangkah-Tegal regency.

For health workers, it is recommended to improve care services for pregnant women, especially in an effort to reduce the incidence of LBW, both from the aspect of knowledge, efforts to provide health education about healthy pregnancies including gestational age at healthy reproductive age, parity and spacing of pregnancies in accordance with government recommendations. and adequate antenatal visits to prevent the incidence of LBW. Recommendations for basic-level health care facilities, such as Puskesmas, are that efforts are needed to provide adequate and standard facilities and infrastructure for handling LBW infants. Efforts are also needed to improve the quality of support staff, by sending these professionals to attend the latest training and seminars on LBW and related matters, so that they can be applied and utilized by the entire team in health facilities in accordance with their authority. For other researchers, it is necessary to conduct similar research with other variables that have not been studied such as nutritional factors, health history, and environmental factors

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Dimensions of factors influencing unmet needs in family planning programs

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ABSTRACT: The achievement of the unmet needs target in the family planning program is a manifestation of the success of the family planning program in increasing strong human resources, national resilience, people's welfare, and ensuring the sustainability of national development. This study aims to analyze the factors influencing the occurrence of unmet needs in the family planning program based on three main dimensions of developing an understanding of public health. This study uses the scoping review method of articles with the theme "family planning". Article searches were carried out through PubMed, Scopus, and Emerald, with inclusion criteria: free full text or open access, systematic review, and meta-analysis, published between 2017–2022, articles in English, and articles sourced from journals. The keywords used in the search are "family planning" AND "unmet needs." The six articles identified show factors that influence unmet needs in the family planning program, namely age, age at first marriage, marital status, employment status, reading ability, education, fear of side effects of family planning, menstrual patterns, sexually transmitted diseases, perceptions of pregnancy risk, prohibition against using contraception, discussion and communication with partners, husband's support, access to family planning information, integrated or integrated family planning service facilities.

1 INTRODUCTION

Unmet needs for family planning is a need for family planning that is not met. The high number of unmet needs for family planning indicates that family planning services have not been able to meet the needs of the community (Statistik 2022). Indonesia's unmet needs in 2019 is 12.10% with a target of 9.91% and unmet needs in 2020 is 13.4% with a target of 8.6% (Indonesia 2020).

The desire of a fertile-age couple age towards the unmet needs for family planning is a form of health promotion behavior. According to Stanhope & Lancaster, 2012, health promotion behavior can be influenced by three main dimensions of public health development, namely the status dimension, structural dimension, and process dimension. The status dimension includes biological aspects (age, parity, reproductive health history, birth

spacing), emotional or psychological aspects (anxiety and motivation), and social aspects (knowledge and family support). Structural dimensions, including the availability of services and the availability of resources or service personnel. The process dimension includes the role of the community, community support or health workers or extension officers, and government support (Stanhope & Lancaster 2015).

2 METHODS

This study aims to analyze the dimensions of factors that influence the unmet needs for family planning based on the three main dimensions of developing an understanding of public health using the scoping review method. Article searches were performed using search engines, including PubMed, Scopus, Emerald, and Science Direct. The inclusion criteria used in the search for articles to be reviewed were free full text with a systematic review and meta-analysis study design or review articles, open access, in English, and published between 2017–2022. The keywords used in the search for articles are “family planning” AND “unmet needs”. Search results for articles with the keyword “family planning” obtained 70,190 articles. After applying the filter according to the inclusion criteria, 58 articles were obtained. Of the 58 articles, identification was carried out by reviewing the titles and abstracts, which were then reviewed for the contents of the articles, and 6 articles that met the criteria were obtained. All identified articles were imported into the Mendeley reference management application, and the same articles were deleted (Figure 1).

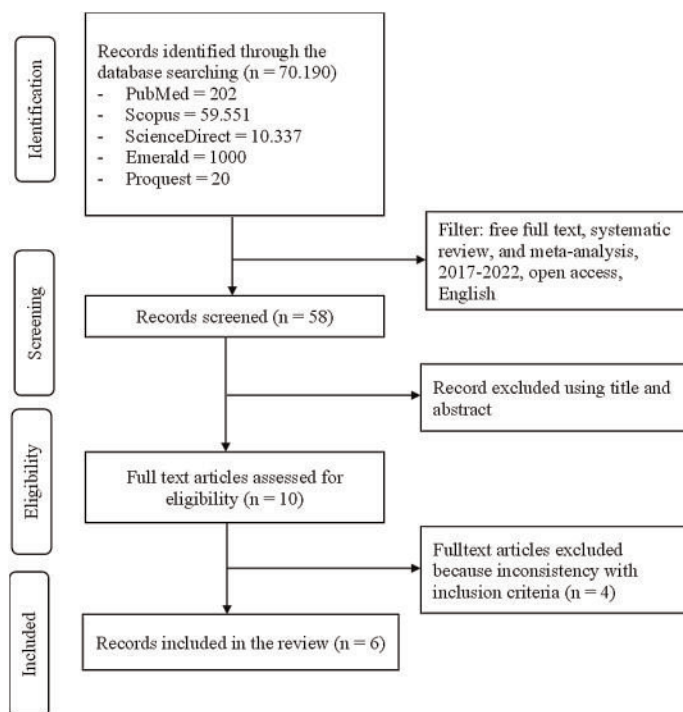


Figure 1. Selection flowchart of scoping review: Dimensions of factors affecting unmet needs in family planning programs.

Table 1. Table of synthesis of scoping review: Dimensions of factors affecting unmet needs in family planning programs.

Author (year)	Research titles	Purpose	Method	Sample	Research result
Gahungu <i>et al.</i> , 2021	The unmet needs for modern family planning methods among postpartum women in Sub-Saharan Africa: A systematic review of the literature	To assess factors affecting the unmet needs and reasons for non-utilization of modern contraceptive methods during the postpartum period in Sub-Saharan African women	Systematic review	19 studies	The results showed that the factors influencing the unmet needs for family planning were fear of side effects of family planning, husband's support, menstrual patterns, perceptions of pregnancy risks, and having taboos.
Getaneh <i>et al.</i> , 2020	Predictors of unmet needs for family planning in Ethiopia 2019: A systematic review and meta-analysis	To identify the predictors of unmet needs for family planning in Ethiopia.	A systematic review and meta-analysis	All observational studies were done on reproductive-age women and reported on the unmet needs for family planning	The results showed that the factors influencing the unmet needs for family planning were age at first marriage, formal education, partner education, discussions with partners
Worku <i>et al.</i> , 2020	Unmet needs for family planning in Ethiopia and its association with occupational status of women and discussion to her partner: a systematic review and meta-analysis	To estimate the pooled prevalence of unmet needs for family planning and its association with the occupational status of women and discussion with her partner among fecund women in Ethiopia	A systematic review and meta-analysis	9 studies	The results showed that the factors that influence family planning unmet needs, namely marital status, employment status, communication with partners
Mekie <i>et al.</i> , 2021	The Level of Unmet needs for Family Planning and Its Predictors among HIV-Positive Women in Ethiopia: A Systematic Review and Meta-Analysis	To assess the level of unmet needs for family planning and its predictors among HIV-positive women in Ethiopia	Systematic review and meta-analysis	Nine primary studies	The results showed that the factors influencing the unmet needs for family planning were age, reading ability, communication with partners, and access to family planning information.
Grant-Maidment <i>et al.</i> , 2022	The Effect of Integration of Family Planning Into HIV Services on Contraceptive Use Among Women Accessing HIV Services in Low and Middle-Income Countries: A Systematic Review	To determine whether integration of FP into HIV testing and care results in increased use of contraception, a reduction in unmet needs for FP, improved use of safer conception methods, and a reduction in unintended pregnancies in low and middle-income countries	Systematic review	13 studies	The results showed that the factors that influence the unmet needs for family planning are age, integrated family planning service facilities, or integrated family planning with HIV
Kefale <i>et al.</i> , 2021	Unmet needs for family planning among reproductive-age women living with HIV in Ethiopia: A systematic review and meta-analysis	To estimate the pooled prevalence of unmet needs for family planning among reproductive-age women living with HIV in Ethiopia	Systematic Reviews and Meta-Analyses	7 studies	The results of the study showed that the factors influencing the unmet needs for family planning, namely sexually transmitted diseases (HIV)

3 RESULTS AND DISCUSSION

A scoping review was carried out by synthesizing articles using a literature synthesis matrix. Based on the results of the identification of 6 articles that met the inclusion criteria, it was found that the factors that influence unmet need for family planning can be categorized into three main dimensions of public health development, namely age, age at first marriage, marital status, employment status, ability to read, education, fear of side effects Family planning, menstrual patterns, sexually transmitted diseases, perceived risk of pregnancy, abstinence from using contraception, discussion and communication with partners, husband's support are status dimensions (Gahungu *et al.* 2021; Getaneh *et al.* 2020; Grant-Maidment *et al.* 2022; Kefale *et al.* 2021; Mekie *et al.* 2021; Stanhope & Lancaster 2015; Worku *et al.* 2020). The results of other studies indicate that the factors that influence unmet needs for family planning are age at first marriage, education, sexual support, access to information media, age, socioeconomic conditions, media exposure, and government involvement in policymaking. In addition, factors that influence family planning unmet needs are norms, equality of relations, and community dynamics. Access to integrated or integrated family planning information and family planning service facilities is a structural dimension. In this study, there was no process dimension found, because in this study there were no articles that found community role factors, especially family planning counselors, community support or health workers, and government support that influenced unmet need for family planning. = (Asmamaw & Negash 2023; Assefa *et al.* 2023; Phiri *et al.* 2023; Sileo *et al.* 2022).

Unmet needs indicate that individual or community health behavior in family planning programs is not optimal. Unmet need for family planning is caused by the lack of perceptions of a fertile-age couple about the benefits, risks, supporting and inhibiting factors of family planning programs. Fertile-age couples perceptions of family planning programs can foster the readiness, motivation, and self-confidence of a fertile-age couple in family planning programs (Stanhope & Lancaster 2015). The perception of fertile-age couple is related to the level of women's understanding and awareness of family planning programs. Efforts to increase women's understanding and awareness of family planning programs can be done using an individual-centered approach by increasing access to family planning information (Senderowicz & Maloney 2022).

4 CONCLUSION

Factors that influence unmet need for family planning are age, age at first marriage, marital status, employment status, ability to read, education, education, fear of side effects of family planning, menstrual patterns, sexually transmitted diseases, perceptions of risk of pregnancy, prohibition of contraceptive use, discussions and communication with partners, husband support, access to family planning information and integrated or integrated family planning service facilities.

ACKNOWLEDGMENT

The author would like to thank all colleagues from Diponegoro University, Sebelas Maret University, and the National Research and Innovation Agency who have contributed to the research and writing stages of this article.

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Emotional eating and obesity in adolescents: A systematic review

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ABSTRACT: Obesity is one of adolescent’s nutritional problems that increases the risk of degenerative disease. One of the factors that causes adolescent obesity is emotional eating. Adolescents are a stress-prone age group and at a sufficiently high risk of experiencing emotional eating. This study aims to analyze the relationship between emotional eating and obesity among adolescents. The literature was searched using electronic databases (SpringerLink, PubMed, and Science Direct) using the following keywords: “Emotional eating”, “Obesity”, and “Adolescents”. PICO (population, intervention, control, and outcomes) tables were used as a framework for this literature review. Eligible articles were included if they were: published from 2012 to 2022, written in Bahasa or English, discussing the relationship between emotional eating and obesity in adolescents. Based on the literature that was reviewed, emotional eating increases unhealthy food consumption among adolescents and is linked to the tendency for emotional eaters to overeat and consume unhealthy foods, high in fat and sugar. High consumption of fat and sugar would increase the risk of obesity in adolescents. This review concludes that emotional eating is significantly related to obesity in adolescents.

1 INTRODUCTION

Adolescence is a transition period from childhood to adulthood characterized by physical and emotional changes (WHO 2021). Changes that occur rapidly cause various problems for adolescents, so at this time, individuals will be vulnerable to experiencing emotional disorders such as depression, anxiety, and stress disorders (Michels 2012). One of the effects of this emotional disorder is changes in negative eating behavior (Wardle 2011).

The response in the form of changes in eating behavior is referred to as emotional eating (Arnow 1995). Individuals experiencing emotional discomfort may turn to emotional eating as a coping mechanism. Adolescents with emotional eating disorders frequently eat over-sweetened and high-energy foods and beverages. According to some studies, snacking more regularly is linked to higher body weight and a higher risk of becoming overweight

and obese in people of different ages (Barnes 2015; Gunes 2012; Smetanina 2015). Limbers and Summers (2021) conducted a systematic review to assess the association between emotional eating and weight status in adolescents; the findings are inconsistent, and the results do not support a relationship between emotional eating and weight status in adolescents.

According to WHO, obesity has become a global problem. Obesity is also an indirect cause of increased mortality rates. Based on data from the Global Burden of Disease, in 2017, obesity caused 4.7 million deaths worldwide. Obesity contributed to 5.5% of deaths compared to underweight which only contributed to 0.7%. Adolescents between the ages of 15 and 19 who are considered overweight or obese represent 340 million (WHO 2018). Adolescents who are overweight or obese are more likely to suffer the same problems as adulthood and develop various chronic diseases, such as coronary heart disease, type 2 diabetes, and several types of cancer (Tobias & Hu 2018). Moreover, no systematic review analyzed the relationship between emotional eating and obesity in adolescents. The purpose of this study is to inform future research related to emotional eating and obesity, and adolescents.

2 RESEARCH METHODS

The research articles were searched using Springer, PubMed, and Science Direct databases, which it published from January 2012 until November 2022. Emotional eating, obesity, and adolescent are the search terms used to find the relevant articles. The literature review will be examined using a matrix table. This review was accessible both to the cross-sectional and longitudinal research designs. This study’s inclusion criteria are an English-language article discussing the effect of emotional eating on adolescent obesity, an English-language full-text publication, and human participants. Studies were ruled ineligible if their subjects were not adolescents if the outcome was not obesity, and if experimental research methods were employed. The collected articles will be screened by title and abstract based on inclusion and exclusion criteria. Strategies for literature review is shown in PICO table (Table 1).

Table 1. PICO table.

PICO	Term	Alternative
Patients/ population/ Problem	Adolescents	Obesity
Intervention	The effect of Emotional eating on obesity	
Comparison	–	
Outcomes	Adolescents have no emotional eating and have normal weight	Healthy eating behavior and not obese

According to the findings of a search conducted on Springer, PubMed, and Science Direct using the keywords “emotional eating”, “obesity”, and “adolescent”, a total of 2004 journals were discovered. The knowledge in the area of screening abstracts and titles of 1239 eliminated articles led to the completion of screening to 765 journals. According to the screening, 23 articles were selected for feasibility testing, and the remaining 12 articles completed the review inclusion criteria.

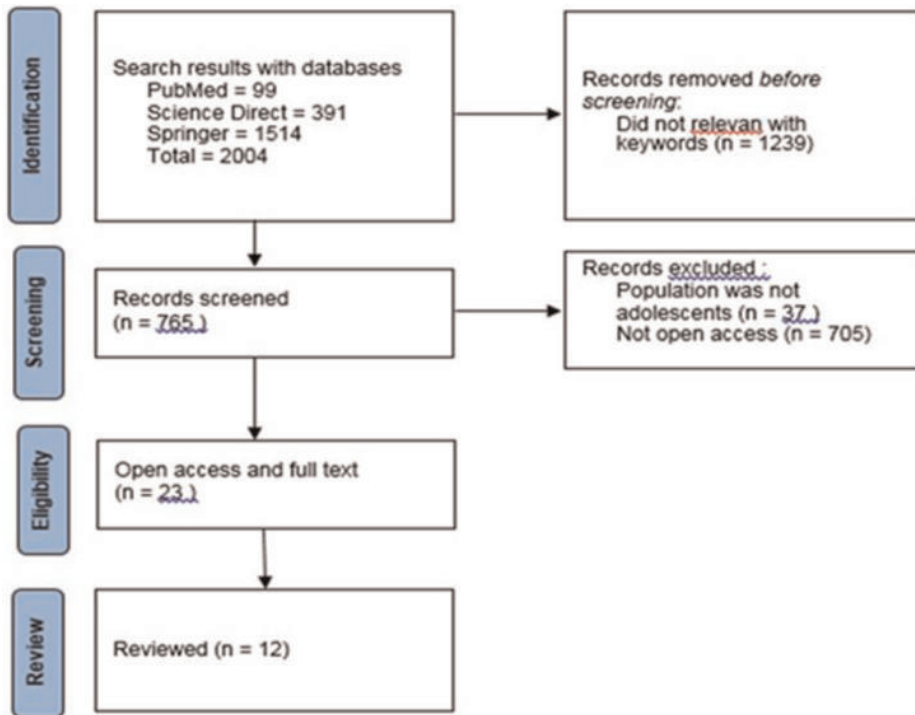


Figure 1. Flowchart of systematic review according to PRISMA.

Table 2. The summary of selected studies.

No	Author	Title	Research purpose	Method research	Result
1.	Fox <i>et al.</i> 2015	Depression, Anxiety, and Severity of Obesity in Adolescents: Is Emotional Eating the Link?	Characterized the impact of depression and anxiety on the severity of obesity among adolescents and determine the extent to which emotional eating mediates the relationship between depression and/or anxiety and the degree of obesity	Cross sectional	Depression and anxiety are associated with more severe obesity among adolescent, but emotional eating was not a mediator between depression/anxiety and severity of obesity
2.	Sze <i>et al.</i> 2021	Prevalence of negative emotional eating and its associated psychosocial factors among urban Chinese undergraduates in Hong Kong: a cross-sectional study	Examined the prevalence and factors associated with emotional eating among urban Chinese university students.	Cross sectional study	Anxiety levels were not independently associated with negative emotional eating for either gender. Both male and female students with negative emotional eating had significantly lower self-perceived health scores, higher body mass index, and lower life satisfaction scores.

(continued)

Table 2. Continued

No	Author	Title	Research purpose	Method research	Result
3.	Hootman <i>et al.</i> 2018	Stress and Psychological Constructs Related Eating Behavior Are Associated with Anthropometry and Body Composition in Young Adults	This study was to evaluate sex differences in stress, emotional eating, tendency to overeat, and restrained eating behavior, and determine whether the psycho-behavioral constructs assessed immediately prior to starting college are associated with anthropometry and adiposity at the start of college, and with first-semester weight gain	Longitudinal prospective cohort study	In sex-adjusted linear regression models, baseline TFEQ disinhibited and emotional (DE;EE) eating sub-scales were positively associated with baseline weight (P = 0.003;DE, P = 0.014;EE), body mass index (BMI, P = 0.002;DE, P = 0.001;EE), WC (P = 0.004; DE, P = 0.006;EE) and DXA fat mass index (P = 0.023;DE, P = 0.014;EE). Baseline PSS was positively associated with subsequent changes in weight and WC among males only (weight Pinteraction = 0.0268;WC Pinteraction = 0.0017).
4.	Nogay. 2017	The role of psychological eating styles in obesity among Turkish adolescents: A cross-sectional study	This study aimed to determine the relationship between eating behaviors and adiposity indicators including body mass index, waist-hip ratio, and waist-height ratio in adolescents.	Cross-sectional	Cognitive restraint and emotional eating scores of females were significantly higher than those of males. Cognitive restraint scores of participants who were thin according to the body mass index were significantly lower than participants who were at normal weight and who were overweight. Body mass index was significantly and positively correlated to cognitive restraint and emotional eating subscales, whereas there was a significant negative correlation between emotional eating and waist-height ratio. Cognitive restraint regarding food intake and tendency to emotional eating increased the risk of obesity. Significantly (P < .05), lower egg consumption, higher grain consumption, and poorer food guide score were all related to a later chronotype. Significant (P < .05) relationships between a higher value of Social Jetlag and lower total energy intake, lower consumption of grains, and higher consumption of sugar and sweets were also revealed by multivariable linear regression.
5.	Fanton <i>et al.</i> 2021	Alexithymia in Obese Adolescents is Associated with Severe Obesity and Binge Eating Behavior	This research was to study the occurrence of alexithymia in obese adolescents' intake among university students.	Cross sectional study	Significantly (P < .05), lower egg consumption, higher grain consumption, and poorer food guide score were all related to a later chronotype. Significant (P < .05) relationships between a higher value of Social Jetlag and lower total energy intake, lower consumption of grains, and higher consumption of sugar and sweets were also revealed by multivariable linear regression.
6.	Sukariyah & Sidani 2014	Prevalence of and Gender Differences in Weight, Body, and Eating Related	As a first step in developing school counseling interventions to assist	Cross-sectional	Adolescents of normal weight scored higher on measures of body esteem,

(continued)

Table 2. Continued

No	Author	Title	Research purpose	Method research	Result
		Perceptions among Lebanese High School Students: Implications for School Counseling	students in creating a more positive body image, the study's objective is to investigate the prevalence of and gender variations in weight, body, and eating-related attitudes among Lebanese high school students.		while those who were overweight were more likely to report engaging in binge eating habits. Teenagers who are overweight report having greater actual and ideal body shapes, show more body dissatisfaction and aggravation at the real-ideal difference, attempt more weight loss, and feel more familial pressure to lose weight than their normal weight peers.
7.	Ismail <i>et al.</i> 2021	Psychosocial Factors Affecting Dietary Habits Of University Students: A Cross-sectional Study	This study attempts to analyze the impact of psychosocial factors on university students' eating habits.	Cross-sectional	Moreover, one-third of individuals (37.5%) were categorized as overweight or obese, while 39.1% acknowledged rarely investing in routine physical activity. Less than half of the respondents ate breakfast every day (45.4%), and 83.2% drank less than 2 liters of water every day. Fruits and vegetables were ingested daily by only 28.7% and 34.0% of participants, respectively. Nearly 80% of subjects ate while they were bored, 83.7% when they were joyful, and 56.5% when they were depressed. Participants who did not live with their family ($p < 0.001$), smoked ($p < 0.001$), did not participate in physical activity ($p < 0.001$), and reported eating impulsively ($p < 0.007$) scored significantly worse on the eating habits scale.
8.	Jääskeläinen <i>et al.</i> 2014	Stress-related Eating, Obesity, and Associated Behavioral Traits in Adolescents: A Prospective Population-based Cohort Study	This study intends to investigate the prevalence of strain eating and its relationships to nutritional and other health behaviors in 16-year-olds and overweight, obesity, and abdominal obesity.	Study population	Stress-related eating is every day among 16-year-old girls. It is related to obesity as well as poor nutritional and other health behaviors in both sexes, but intrauterine characteristics may not appear to be a factor.
9.	Wang <i>et al.</i> 2020	Relationships among weight stigma, eating behaviors and stress in adolescents in Wuhan, China	This study aimed to investigate the links between weight stigma, eating habits, and stress, as well as the role of stress in regulating the relationship between body image and eating behaviors.	Cross-sectional	Regardless of body mass index, correlational regression analyses revealed that perceptions of weight stigma substantially predicted emotional and uncontrolled eating (BMI).

(continued)

Table 2. Continued

No	Author	Title	Research purpose	Method research	Result
10.	Roy <i>et al.</i> 2021	Perceived stress, eating behavior, and overweight and obesity among urban adolescents	This review investigated the prevalence of overweight/obesity and its risk factors, as well as perceived stress through eating habits and physical activity among Bangladeshi urban adolescents attending high school and college.	Cross-sectional	Perceived stress was linked to eating habits and body mass index in a significant way, while physical activity was linked to both being overweight or obese and having a lot of stress.
11.	Durmaz <i>et al.</i> 2022	Effect of emotional eating and social media on nutritional behaviour and obesity in university students who were receiving distance education due to the COVID-19 pandemic	This study intends to investigate the influence of social media and emotional eating on eating behavior and obesity among university students enrolled in distance-learning programs during the pandemic.	Cross-sectional	Social media influences eating behavior, BMI, and emotional eating among students who obtained distance education. In addition, these impacts may raise the likelihood of being overweight or obese.
12.	Jung <i>et al.</i> 2017	Binge eating is associated with trait anxiety in Korean adolescent girls: a cross-sectional study	This study investigated the association between binge eating and depression, trait anxiety, and perceived stress among Korean adolescents.	Cross-sectional	The group that engaged in binge eating had a greater BMI than the control group.

Table 3. Critical appraisal using Jadad scale.

No	Item related directly to the control of bias using the jaded scale	Fox <i>et al.</i> 2015	Sze <i>et al.</i> 2021	Hootman <i>et al.</i> 2018	Nogay 2017
1	Was the study designed as randomized? Method of randomization (appropriate/inappropriate)	0	0	0	1 1
2	Was the study designed as double-blind? Method of double blinding (appropriate/inappropriate)	0	0	0	0
3	Was there a description of the withdrawals and dropouts?	1	1	0	0
Other markers not related directly to the control of bias					
1	Were the objectives of the study defined?	1	1	1	1
2	Were the outcome measures defined clearly?	1	1	1	1
3	Was there a clear description of the inclusion and exclusion criteria?	1	1	0	1
4	Was the sample size justified (e.g., power calculation)?	1	1	0	1
5	Was there a clear description of the interventions?	1	1	1	1
6	Was there at least one control (comparison) group?	0	0	1	0
7	Was the method used to assess adverse effects described?	0	0	0	0
8	Were the methods of statistical analysis described?	1	1	1	1
Total Score		7	7	5	8

(continued)

Table 3. Continued

No	Item related directly to the control of bias using the Jaded scale	Fanton <i>et al.</i> 2021	Sukariyah & Sidani 2014	Ismail <i>et al.</i> 2021	Jääskeläinen <i>et al.</i> 2014
1	Was the study designed as randomized? Method of randomization (appropriate/inappropriate)	0	1 1	1 1	0
2	Was the study designed as double-blind? Method of double blinding (appropriate/inappropriate)	0	0	0	0
3	Was there a description of the withdrawals and dropouts?	1	0	1	1
Other markers not related directly to the control of bias					
1	Were the objectives of the study defined?	1	1	1	1
2	Were the outcome measures defined clearly?	1	1	1	1
3	Was there a clear description of the inclusion and exclusion criteria?	0	0	0	0
4	Was the sample size justified (e.g., power calculation)?	1	1	1	1
5	Was there a clear description of the interventions?	0	0	1	1
6	Was there at least one control (comparison) group?	0	1	0	1
7	Was the method used to assess adverse effects described?	0	0	0	0
8	Were the methods of statistical analysis described?	1	1	1	1
Total Score		5	7	8	7
No	Item related directly to the control of bias using the Jaded scale	Wang <i>et al.</i> 2020	Roy <i>et al.</i> 2021	Durmaz <i>et al.</i> 2018	Jung <i>et al.</i> 2017
1	Was the study designed as randomized? Method of randomization (appropriate/inappropriate)	0	0	1 1	1 1
2	Was the study designed as double-blind? Method of double blinding (appropriate/inappropriate)	0	0	0	0
3	Was there a description of the withdrawals and dropouts?	1	1	1	1
Other markers not related directly to the control of bias					
1	Were the objectives of the study defined?	1	1	1	1
2	Were the outcome measures defined clearly?	1	1	1	1
3	Was there a clear description of the inclusion and exclusion criteria?	0	1	1	0
4	Was the sample size justified (e.g., power calculation)?	1	1	1	1
5	Was there a clear description of the interventions?	1	1	1	1
6	Was there at least one control (comparison) group?	0	0	0	0
7	Was the method used to assess adverse effects described?	0	0	0	0
8	Were the methods of statistical analysis described?	1	1	1	1
Total Score		6	7	9	8

3 RESULTS

Of the 12 studies in this review, one found no relationship between emotional eating and obesity in adolescents. The other eleven studies found that emotional eating was correlated with obesity in adolescents.

4 DISCUSSION

The systematic review's objective is to examine how emotional eating affects adolescent obesity. A review of 11 studies shows an association between emotional eating and adolescent obesity risk. Considering affects a person's capability for awareness of these internal cues, emotional eating has been linked to decreased awareness of inner hunger and satiety cues (Tan 2014). Furthermore, it was discovered that those who had binge-eating episodes ate emotionally because they could not control their appetites (Goossens 2007).

The most common causes of emotional eating include genetic abnormalities, emotional dysregulation, and alexithymia. Genetic variables were linked to the Hypothalamic Pituitary Adrenal (HPA) response to stress by cortisol release through a system known as the serotonergic brain system. The 5-HTT-SLC6A4 serotonin transporter gene was required to control serotonin secretion in the serotonergic brain system, which will stabilize hunger and body weight. Serotonin secretion will decrease if there is a disruption in the serotonergic brain system, such as polymorphisms in the 5-HTTLPR allele gene, resulting in depressive symptoms and emotional eating disorders (Van Strein 2010).

Palatable meals, often known as comfort foods, have a higher proportion of sugar and fat that provide pleasure when consumed. Individuals feeling anxious tend to consume more appetizing meals, which might result in increased weight and obesity (Laitinen 2002).

5 CONCLUSIONS

This review concludes that emotional eating was significantly correlated with obesity in adolescents.

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Implementation of the community development model at the *Jogo Tonggo* task force in controlling COVID-19

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ABSTRACT: The effective control of COVID-19 depends on the active involvement and empowerment of the community. In the Central Java region, this objective is achieved through the implementation of the *Jogo Tonggo* Task Force. Therefore, this research aimed to examine the implementation of a community development model through the *Jogo Tonggo* Task Force in controlling COVID-19. The study adopted a phenomenological approach and was conducted in the Karanganyar Regency from July to November 2022. Participants were selected through purposive sampling, with 31 members of the *Jogo Tonggo* Task Force participating. Data was collected through both document review and in-depth interviews. The analysis involved descriptive, reduction, essence, and intentionality methods. The results showed that the community has plans in place to improve their approach to controlling COVID-19. These plans involve improving organization, providing mutual support, increasing cooperation and coordination, developing leadership skills, building capacity, securing resources, reaching out to others, and setting a good example. The organization also wants to make changes by identifying problems, finding solutions, evaluating their success, and institutionalizing successful changes. Emotional support is provided through empathy, compassion, and offering both moral and material assistance to help prevent feelings of isolation. Practical support includes providing food and masks, ensuring hand washing facilities are available, and promoting social distancing during religious gatherings. Information is also provided to offer advice, suggestions, and keep people informed. Assessment support involved the provision of feedback, sanctions, and warnings. The *Jogo Tonggo* Task Force as a model of community development in controlling COVID-19 consists of three dimensions: (i) community organization for local development, (ii) organizational change involving the definition of the problem, initiating action, and implementation as well as institutionalization of change, (iii) social support in the form of appraisal, instrumental, informational and emotional support.

1 INTRODUCTION

The Indonesian government has classified the COVID-19 outbreak as a non-natural disease and is taking a holistic approach through community development, which involves all components of society (COVID-19 Handling Task Force 2022). Controlling COVID-19 is largely influenced by the policies set by the government and the absence of community development that is guided by proven theories and models. To be effective, it is important to have the participation and involvement of the community, as this empowers them to take action.

The *Jogo Tonggo* Task Force, also known as the Neighbor Guard Task Force, has been tasked with promoting cooperation among residents to combat COVID-19. It brings together the activities of social organizations at the RW level and beyond, and empowers citizens at the RT/RW level to independently fight the pandemic. The aim of encouraging active participation by citizens is to protect one another from transmission by paying more attention to those who are infected and avoiding stigma, as outlined in Central Java Governor Instruction No. 1 of 2020.

The success of handling COVID-19 problems at the RT/RW level largely depends on the ability of local leaders to organize and empower their community members. The existence of the *Jogo Tonggo* Task Force can greatly improve the community-based handling of the pandemic by accelerating the control at the village level. As a form of volunteer-based community development, it is an effort to overcome the crisis of a social activity and create community resilience as a process of adaptation in threatening situations (NICE 2008). Control of the COVID-19 pandemic requires collaboration among all members of the community, with a focus on government policies, guidance, and mobilization. However, a community-based approach grounded in established theories and models is also crucial.

The community development approach used in this research is based on various theories, including health promotion (Frost & Zuckerman 2008), community organizing (Rothman *et al.* 2019; Bezboruah 2013), organizational change (Gwaka *et al.* 2016; Higgins & Bourne 2018; Hussain *et al.* 2016), and social support models (Berkman & Glass 2000) at the organizational and community levels.

Furthermore, Rothman (2019) categorized community organizing into social planning, locality development, and social action models. Organizational change theory covers defining the problem, initiation, implementation, and institutionalizing change (Gwaka *et al.* 2016; Higgins & Bourne 2018; Hussain *et al.* 2016). Additionally, social support is categorized into emotional, instrumental, informational, and appraisal support.

Based on the above discussion, the *Jogo Tonggo* Task Force has the potential to enhance the community's efforts in controlling the spread of COVID-19 and treating affected residents. However, there is a need for further research to investigate the dimensions that contribute to the success of the *Jogo Tonggo* Task Force. Additionally, the impact of the *Jogo Tonggo* Task Force on fostering community resilience has yet to be scientifically established. Thus, the objective of this research is to examine the implementation of a community development model in addressing the COVID-19 pandemic in Karanganyar Regency, Central Java, Indonesia.

2 METHODOLOGY RESEARCH

The inadequate number of healthcare officers assigned to control COVID-19 in Karanganyar Regency, combined with limited access to health facilities and the vast area, makes it challenging for the government to effectively manage the pandemic. To address this issue, the *Jogo Tonggo* Task Force was established at the RW level based on Central Java Governor's Instruction No. 1 of 2020, which relies on community participation. Preliminary research suggests that the control measures taken by the *Jogo Tonggo* Task Force have been successful in reducing the number of cases.

This research is using a phenomenological approach to gain insight into how the participants interpret and understand the essence of the COVID-19 control efforts in Karanganyar Regency, Central Java Province, Indonesia. Data collection was conducted for a period of 5 months, from July 2022 to November 2022. The population studied are the administrators of the *Jogo Tonggo* Task Force in Karanganyar Regency, and a purposive sampling method was used to select 31 informants from 5 sub-districts. The data was collected through a review of documents and in-depth interviews. The community development dimension includes organizing, organizational change, and social support.

The sample participants were chosen through a purposive sampling method, which means the selection was based on the suitability of the characteristics of the participants to meet certain criteria (Creswell 2009). The participants were selected based on their categories as community and health workers, as well as their living area (rural or urban).

To collect data for the research, guidelines were created for both document review and in-depth interviews. The data was then analyzed using a descriptive, reduction, essence, and intentionality method to identify major categories and themes (Graneheim & Lundman 2004). This information was then summarized and codes were created for each unit of meaning.

3 RESULTS OF THE RESEARCH

3.1 Document review

The *Jogo Tonggo* Task Force is responsible for overseeing the community and preventing the spread of COVID-19. In addition, it coordinates efforts among social groups such as Karang Taruna, Dasa Wisma, Posyandu, residents at the RW level, and outside organizations. The Task Force is divided into four sectors, namely health, economy, security, and entertainment, as outlined in the Central Java Governor's Instruction No. 1 of 2020. It is led directly by the chief of RW and the deputies from all the chiefs of RT in the RW area. The Task Force has four sections, namely the *Jogo Tonggo* Health, Economic, and Entertainment Task Forces, except *Jogo Tonggo* Social and Security Task Force, with 5 members. The coordinators of the four Task Forces are selected from the elements of the leadership of social group organizations and competent residents in the RW area.

Table 1. Characteristics of participants.

Characteristics	Category	N	%
Sex	Man	20	64.52
	Women	11	35.48
Age	26–35 years old	3	9.68
	36–45 years old	8	25.81
	46–70 years old	20	64.51
Address	Villages	24	77.42
	Sub-Districts	7	22.58
Education	Senior High School	11	35.48
	Graduated D3 (associate degree) in Midwifery	7	22.58
	Undergraduate degree	13	41.93
Job	Village Midwife	7	22.58
	Village Apparatus	9	29.03
	Government employees	6	19.35
	Self-employed	5	16.14
	Housewives	4	12.90

3.2 In-depth interview results

How is the implementation of the community development model in the *Jogo Tonggo* Task Force in controlling COVID-19?

3.2.1 How is social action implemented in controlling COVID-19 spread?

To effectively control the spread of COVID-19, the community plays an active role through social action. This involves discussions among community and health workers, taking local culture into account and meeting the needs of the community. Effective coordination between health workers, healthcare staff, and community leaders is crucial in this effort.

3.2.2 How is social planning implemented in controlling COVID-19?

Controlling COVID-19 through social planning is a shared responsibility between the community and the task force. The community is educated and informed about what to do, and the task force conducts intensive socialization.

3.2.3 How is local development implemented in controlling COVID-19?

Local development involves community involvement, decision-making through agreement, information sharing, working together, involving local leaders, and helping each other.

3.2.4 *How is an organizational change implemented in controlling COVID-19?*

Organizational changes in controlling COVID-19 are based on government instructions and resident reports. Solutions are sought, problems are assessed and addressed, COVID-19 incidents are monitored, as well as innovations are developed through evaluation, community input, and coordination.

3.2.5 *The implementation of social support in controlling COVID-19*

3.2.5.1 *How is emotional support in controlling COVID-19?*

The implementation of emotional support in controlling COVID-19 includes working with heart and giving empathy to the community through visiting residents who tested positive, providing groceries for self-isolated residents, providing moral support and enthusiasm, avoiding stereotyping residents who tested positive, avoiding discrimination among citizens, approaching residents morally and face to face, setting an example, providing good service, benefitting the community, involving the community, and avoiding the practice of coercion to the community.

3.2.5.2 *How is the instrumental support in controlling COVID-19?*

Instrumental support is implemented by covering mask assistance, providing hand-washing facilities, and obeying physical distancing regulations in places of worship (mosques).

3.2.5.3 *How is informational support in controlling COVID-19?*

The implementation of support is conducted by conveying information in a polite and easy-to-understand language, persuasively, and without sanctions for the residents to feel cared for and have friends who can give advice.

3.2.5.4 *How does appraisal support affect COVID-19 control?*

The assessment of support in controlling COVID-19 involves providing feedback, monitoring the community and responding to complaints, giving persuasive warnings without sanctions or suggestions. The members who disobey the regulations may face reprimands, fines, mandatory mask-wearing, and a 14-day quarantine for travelers.

4 DISCUSSION

Community development involves organizing, managing changes in organizations, and providing social support. Organizing means that community members work together to address social problems and bring about changes in policies and systems at the local, regional, and national level. It involves collective action and ongoing investigation of shared concerns (Brown *et al.* 2003).

This research found that the community is receptive to and supportive of the *Jogo Tonggo* Task Force initiative. Furthermore, the response to the program has been overwhelmingly positive. The community has come together to offer both tangible and service-oriented support.

The community carries out planning without involving any outside parties. It is conducted through deliberations to build collective agreement, pay attention to local culture, share responsibility, accommodate community aspirations, create coordination among health workers, healthcare cadres, and community leaders, communicate with residents, and go to the field. Furthermore, socialization involving the community is performed by inviting everyone to participate in meetings, provide information for each other, involve local leaders, set an example, and help each other. Community readiness to respond to and recover from the pandemic impacts human health and community resilience (Walton *et al.* 2021).

This research found that the implementation of organizational changes in controlling COVID-19 was carried out by elaborating the results of observations, input, and reports from residents who were confirmed and tested positive. Furthermore, government instructions as well, examining the causes of the problem and determining priorities, seeking

solutions, starting with issues with big impact, fixing deficiencies through deliberations, education, and coordination, and developing innovation (Asad *et al.* 2018).

Choflet *et al.*'s research (2021) found that a planned organizational change model can be used to identify a set of principles during the pandemic crisis. Complex Adaptive Systems (CAS) offer a way to deal with crisis conditions. This system requires constant assessment, high-level communication, repetition, reflection, and learning cycles. Healthcare providers are experiencing periods of crisis that need to be recognized and managed proactively through continuous organizational change using a timely combination of traditional methods, a complexity approach, with the flexibility and ethical considerations of a crisis management strategy requiring leadership skills in decision-making at the local level, and with preferences using inclusive as well as adaptive leadership styles.

The *Jogo Tonggo* Task Force, as a Culture-Centered Approach (CCA), puts forward the role of community organizing as a space to identify health and well-being challenges as well as co-create community-based solutions (Dutta *et al.* 2020).

This research found that the *Jogo Tonggo* Task Force in Karanganyar Regency, Central Java Province, Indonesia, successfully controls COVID-19 through community development that consists of three dimensions: organization, organizational change, and social support. The community organizes without outside help and the process of organizational change involves defining the problem, starting action, and institutionalizing change. Meanwhile, social support involves various forms of support such as appraisal, instrumental, informational, and emotional. The research results show that the community accepts and supports the Task Force and actively participates in providing material and service assistance.

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Parents' perception of cough and cold self-medication of age under five

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ABSTRACT: It has become usual practice to treat mild illnesses in children at home. When it comes to young children, such as those under the age of five, self-medication is widespread and a serious problem. The study seeks to understand how parents view children self-medicating for colds and coughs. The design of the research method is scoping review using the PRISMA-ScR checklist Joanna Briggs Institute (JBI) critical appraisal tool, with a PEOs framework, using three databases from PubMed, NCBI, and ResearchGate. Inclusion criteria are original English articles that can be accessed between 2018 and 2022. From 384 papers, we found eight that are pertinent to our study goals. The findings indicated that most parents have a reasonable understanding of and perception of self-medication activities. The idea that self-medication can treat colds and coughs is a significant motivator for this practice. The majority of responders thought self-medication was just as effective as prescribed drugs and was more time- and money-efficient. The conclusion is that most respondents thought self-medication was equally effective to prescription medication, cheaper, and time-saving. To prevent its impending or widespread adverse effects, it is advised that responsible self-medication practice be advocated for during the formal training of these future health professionals.

1 INTRODUCTION

It is becoming more popular to treat children's mild illnesses at home. When it comes to tiny kids, such as those under the age of five, self-medication is a widespread habit around the world, and the inappropriate use of medications is concerning. The study seeks to understand how parents feel about using cough and cold self-medication. Design of the research method is scoping review using the PRISMA-ScR checklist Joanna Briggs Institute (JBI) critical appraisal tool, with a PEOs framework, using 3 databases from PubMed, NCBI, and ResearchGate. Inclusion criteria are original English articles that can be accessed between 2018 and 2022. From 384 papers, we were able to find eight pertinent to the study's goals. Cross-sectional studies, systematic reviews, and qualitative research are all types of study. The findings indicated that most parents have a reasonable understanding of and perception of practices involving self-medication. Self-medication practice is stimulated mainly by the idea that it can alleviate colds and coughs. Results showed a favorable opinion of self-medication, and respondents were found to be entirely

engaged in its use. Most respondents said self-medication was just as successful as a prescription medication in terms of cost, time savings, and cost. The conclusion is that most respondents thought self-medication was just as successful as a prescription medication in terms of cost, time savings, and efficiency. It is advised that advocacy be made for responsible self-medication during the formal training of these future health professionals to prevent its impending or widespread detrimental effects (Ahmed *et al.* 2021; Huffman 2003; Widayati *et al.* 2011). The World Health Organization (WHO) defines self-medication as “the selection and use of medicines by individuals to treat self-recognized illnesses or symptoms” (Ayosanmi *et al.* 2022; Dilie *et al.* 2017; Lokker *et al.* 2009; Osemene & Lamikanra 2012; Varun & Abha 2015).

In the pediatric population, self-medication refers to giving a child a drug by a caregiver without consulting a doctor (Tarcuc *et al.* 2020). Responsible self-medication uses medicines recognized as safe, effective, and backed by information to guide consumers (Ukwishaka *et al.* 2020). Patients who self-medicate may benefit from quick access to treatment, independence in managing symptoms, cost savings from healthcare access, and fewer visits to health centers. For the community, self-medication may also have benefits like preserving medical resources, reducing time away from work, lowering demand for medical services, and allowing more time for severe conditions. The belief that self-medication is an effective way to manage minor diseases is a significant motivator for this behavior (Akande-Sholabi *et al.* 2021). Self-medication behavior is influenced by prior personal or shared experiences, as well as by positive perceptions of self-medication’s effectiveness, safety, and convenience (Ahmed *et al.* 2021). However, there is a need to know parents’ perceptions of cough and cold self-medication of ages under five. Therefore, we aimed at Parents’ Perceptions of Cough and Cold Self-Medication of Age Under Five.

2 METHODS

The method used in this review is a scoping review using prism-ScR, which is an ideal approach to determine the scope or scope of a collection of literature on a particular theme to provide a broad overview of the researcher. Scoping review aims to map the literature and explore information about research activities related to specific topics. Besides that, scoping reviews can be used to synthesize research evidence. The researchers develop the focus review and search strategy through the PEOs framework (Population, Exposure, Outcome, study design) to arrange and solve the focus review. P (Population) Parents had children age under five, E (Exposure) Cough and cold of self-medication, O (Outcome) Parents’ Perception of Cough and Cold Self-Medication of Age Under Five, Study design: Parents’ Perception of Cough and Cold Self-Medication of Age Under Five (quantitative, qualitative, mixed method). Based on the framework above, the research question was: Parents’ Perception of Cough and Cold Self-Medication of Age Under Five?

The researchers identified the articles using several databases: PubMed, NCBI, and ResearchGate. The relevant article will be included based on inclusion criteria and exclusion criteria, such as Article from 2018–2022 in the English Language, Original articles, Full-text articles, and article which explains Parents’ Perception of Cough and Cold Self-Medication of Age Under. The Exclusion criteria were Opinion papers, systematic reviews, meta-analyses, editor letters, and commentaries. A literature search in this framework uses the research questions to determine the keywords. Keywords in this literature search were parents’ perception of self-medication AND cough and cold AND self-medication age under five. The researchers used a PRISMA flowchart in this study; After the evidence has been selected, the evidence is extracted. At this stage, all articles that have been selected are entered into a table which includes: the article title, author’s name, year, country, purpose, type of research, participants/sample size, and results.

3 RESULTS

Search outcomes the use of those key phrases ended in 384 articles. Then filtering the articles with inclusion and exclusion standards become received 235 articles. Selection of the following article through eliminating duplication with the result of 58 articles. Subsequently, article removal is achieved primarily based on a whole association of 8 articles. Consistent with previous research, respondents had a favorable opinion of self-medication and were actively engaged in its use. The majority of responders thought self-medication was just as effective as prescribed drugs and was more time- and money-efficient.

4 DISCUSSION

Children who self-medicate are especially concerned since they are thought to be more susceptible to drug interactions. To treat their child's illnesses, parents typically give them medications. In recent years, industrialized and developing nations have seen an increase in utilizing pharmaceuticals for self-medication. Most parents in rich or developing nations prefer to treat their child's common illnesses like fever, cough or cold, and diarrhea without seeking medical advice. Among the often-used self-medications are analgesics, antipyretics, anti-inflammatory drugs, and cough and cold remedies (Elong Ekambi *et al.* 2019; Gohar *et al.* 2017; Herzig *et al.* 2022). In addition, many people turned to self-medication for the first time during the pandemic during the lockdown and the ban on dental work. Access to dental care providers was difficult for patients, and numerous elective operations for dental care providers had to be delayed. In order to do this, it was believed that patients would more frequently self-medicate for oral issues. (Sen Tunc *et al.* 2021; Tarcuic *et al.* 2022).

Yu specifically claimed in 2014 that parents from central towns were more aware of antibiotic use's proper indications and side effects. Therefore, village doctors could play a significant role in disseminating knowledge on managing childhood infections, and parents who live in rural villages should receive more health education. Moreover, in other instances, people believed that antibiotics were only effective against viral infections and were unaware of how to use them correctly in cases of fever (Cruz *et al.* 2022; Elong Ekambi *et al.* 2019; Sun *et al.* 2019; Yu *et al.* 2014). In 2017, Gohar said educated parents used self-medication more frequently than less educated and illiterate parents. According to the current study, parents with low to moderate monthly incomes tend to give their kids more self-medication. Gohar added that parents preferred the most typical sickness: Fever, self-treated (94%). Cough, the flu, the common cold, vomiting, and diarrhea were among the other prevalent diseases for which self-medication was regularly used. Antipyretics accounted for 94% of all medications given to children, followed by cough and cold remedies (60%), antimicrobials (34%), and antiemetics (32%). Analgesics (25%), antihistamines (21%), ophthalmic preparations (9%), topical preparations (5%), and ear preparation (3%), in that order, were followed by these (Gohar *et al.* 2017; Yong *et al.* 2015).

Another factor that compelled parents to give their kids self-medication was the perception of illness (35%) that may have been brought on by prior illness-related experience or information. In addition, Tarcuic noted that self-treatment was successful for mothers who encountered a circumstance like this with their first kid. These comments demonstrate that moms may disregard medical advice in favor of oversimplification based on their prior success in curing their kids. This procedure may result in a false positive and extend the child's illness. Moms typically spend more time caring for their children than fathers do, and educated mothers frequently think they know enough about medicine to provide it to their kids (Du & Knopf 2009). The sense of illness (35%) that might be brought on by prior illness experience or knowledge was another factor that compelled parents to self-medicate their children. Tarcuic added that moms had gone through a similar predicament with their first child, and the self-treatment had helped. These comments demonstrate that women

occasionally disregard medical advice in favor of oversimplification to treat their children based on their prior success. This technique can potentially cause misdiagnosis and extend the child's illness. Fathers rarely spend as much time with their kids as mothers do, and educated mothers frequently think they know enough about medicine to give their kids medicine (Parimi *et al.* 2004; Sen Tunc *et al.* 2021). Other factors included financial limitations and a costly doctor consultation price. The parents were obliged to self-medicate due to various factors, including leftover medication from earlier uses. Parents were also a frequent practice storing leftover medication in this way. Most parents are unaware of the sickness condition for which they intended to use the previous drug, so using leftover medication is not a healthy practice. According to Tarciuc, effective health practitioners' behavior, communication, and attitudes might encourage parents to seek only professional medical care, preventing self-medication. Additionally, most parents were unaware of how to store and maintain the stability of medications, mainly regarding antibiotics (Ahmed *et al.* 2021; Gohar *et al.* 2017; Mukattash *et al.* 2020; Tarciuc *et al.* 2020).

5 CONCLUSION

Most respondents believed that self-medication was just as effective as a prescription medication in terms of cost, time savings, and cost. In order to avoid its impending/widespread negative consequences, it is advised that advocacy on responsible self-medication practice be made during the formal training of these future health professionals.

ACKNOWLEDGEMENT

Source of funding: No funding. Conflict of interest declaration: None of the authors has any conflicts of interest to declare. Authorship responsibilities: NBA reviewed the literature, prepared the data, SJ performed the statistical analysis, and NBA wrote the first draft. SJ contributed to study design, data analysis, NBA interpretation, and manuscript preparation. NBA contributed conceptual and statistical advice.

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Systematic review: Parasitic zoonosis with soil as transmission media

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ABSTRACT: Parasitic infections are one of the leading causes of emerging infectious diseases that affect millions of humans in the world. Zoonoses are diseases that can be naturally transmitted from animals to humans and vice versa. Zoonotic diseases can be caused by a range of pathogens including parasites. This study aims to understand the burden of parasitic zoonoses with soil as transmission media. We conducted a literature search using PubMed and Google Scholar. There are primarily Soil-Transmitted Helminth (STH) infections in the tropical and subtropical regions of Asia, the Americas, and sub-Saharan Africa, where warm humid environments, poor hygiene and sanitation, and limited access to safe water sources facilitate helminth survival. In many areas of Indonesia, the environment and socioeconomic conditions are ideal for STH infections. This needs attention for better public health awareness related to hygiene and sanitation for preventing parasitic zoonotic disease incidences both locally in Indonesia and globally worldwide.

1 INTRODUCTION

In the past century, the world has witnessed the emergence of so-called “emerging and re-emerging diseases” (Irwan & Nur Ayini S. Lalu 2020). Parasites and zoonotic diseases are two categories of these emerging and re-emerging diseases. Parasites are organisms that require hosts to meet their metabolic needs and complete their life cycle (Moorhead 2014). The presence of parasites in the body can impact the physiological processes of the host and cause disease. Parasites are one of the causes of emerging infectious diseases that affect millions of humans worldwide, especially in low-income countries. The impacts range from non-clinical infections to severe and sometimes fatal diseases. Currently, parasitic diseases are contributing to negative health outcomes globally, with the annual incidence increasing. Parasitic diseases are found in many tropical countries, including Indonesia (Taylor et al. 2015).

Zoonotic diseases are infectious diseases, caused by microorganisms or parasites, that can be transmitted in various ways from animals (domestic or wild) to humans and vice versa (Rahman et al. 2020). Zoonotic pathogens may be ubiquitous, with both humans and animals experiencing infection due to environmental exposure, such as seen in melioidosis cases (Hubálek 2003). It is estimated that about 60% of all human infections are of animal origin, and 75% of all new infections in humans occur due to zoonoses (Bajkovec et al. 2021). Zoonotic parasitic diseases are caused by parasites that generally have an animal species as the primary host, and humans may be a required or dead-end host (Youssef & Uga 2014). These diseases are often neglected despite posing a significant threat to public health, especially in low and middle-income countries (Devleeschauwer et al. 2014).

Soil is a common source and transmission media for zoonotic pathogens. It is able to provide an optimal environment for parasites, allowing the parasite life cycle to continue (Nugroho 2014). Fecal contamination of soil by humans and animals is a common source of transmission and infection of zoonotic diseases. In daily life, humans may be exposed directly or indirectly to soil-based pathogens via consumption of food, use of water, and inhalation of aerosolized pathogens. While contact with these pathogens may result in non-clinical infections, there is currently an increase in the occurrence of zoonotic diseases with detrimental health impacts. One group of organisms of significance is soil-transmitted helminths (STHs) (Kretchy 2022).

The objective of this study is to understand the burden and describe the incidence of parasitic zoonosis globally and in Indonesia as well as the incidence of parasitic zoonosis with soil as transmission media (i.e., STHs) globally and in Indonesia.

2 METHODS

This systematic review was conducted with the recommendations outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines 2020 expanded version. Systematic literature searches of electronic databases including PubMed and Google Scholar up to 2 June 2022 used the following search terms: “occurrence of parasitic zoonosis disease”, “cryptosporidiosis infection epidemiology”, “nematode infection epidemiology”, “leishmaniasis epidemiology”, “schistosomiasis epidemiology”, “occurrence of lymphatic filariasis worldwide latest update”, “toxoplasmosis epidemiology”, “toxoplasmosis AND Indonesia”, “taeniasis epidemiology”, “cysticercosis epidemiology”, and “filariasis epidemiology in Indonesia”. The following inclusion criteria were included to select articles for literature review: (i) information was provided related to parasitic zoonosis globally and in Indonesia, (ii) information was provided related to parasitic zoonosis with soil as transmission media (STHs) globally and in Indonesia, (iii) it provided sufficient data of Disability-Adjusted Life Year (DALYs), number of cases, number of deaths, number of risks of exposure, and percentage of prevalence. Studies were excluded if: (i) the article was unavailable in English or Indonesian.

3 RESULTS AND DISCUSSION

3.1 Incidence of zoonotic parasitic diseases globally

Over the last few decades, the increase in globalization has led to increased human migration, international trade, climate change and interactions between humans and domestic and wild animals. While these human-animal interactions have led to an increase in zoonotic parasitic diseases, contributing to the global burden of disease, they largely remain neglected tropical diseases. There are five most important zoonotic parasitic diseases, namely cryptosporidiosis, intestinal infections caused by nematodes, leishmaniasis, schistosomiasis, and lymphatic filariasis (Table 1) (Pisarski 2019).

Table 1. Cases of zoonotic parasitic disease globally.

Name of disease	DALYs	Cases	Deaths	Risk of exposure	References
Cryptosporidiosis	8.27 million	Increased by 3/100,000 population	–	–	11,12
Intestinal nematodes	1.97 million		2090	–	13
Ascariasis	–	0.807–1.221 billion	–	–	14
Tricariasis	–	604–795 million	–	–	14
Hookworm	–	576–740 million	–	–	14
Leishmaniasis	–	±12 million	–	>350 million	15
Visceral Leishmaniasis (VL)	–	0.2–0.4 million	–	–	15
Cutaneous Leishmaniasis (CL)	–	> 0.7–1.2 million	–	–	15
Schistosomiasis	4.5 million	>207 million	150,000–280,000	779 million	16
Lymphatic filariasis	–	±199 million (2000) ±51 million (2018)	–	–	17

Cryptosporidiosis, caused by cryptosporidium protozoa, is an infectious disease that occurs globally. The disease affects several groups of vertebrates, including humans. The disease causes acute gastroenteritis, abdominal pain, and diarrhea. In 2010, cases reached 8.37 million DALYs (Pisarski 2019). Worldwide, cases reported in 2018 increased by 3 cases per 100,000 population, some indications (such as clinical symptoms) suggest that the number of infections is very likely to be 100× higher than the reported cases (Gerace et al. 2019).

Nematodes that cause infection and diseases in humans include ascariasis, Tricariasis, enterobiasis, filariasis, strongyloidiasis, trichinosis, angiostrongyliasis (rat lungworm disease), and dirofilariasis. According to the World Health Organization (WHO) in 2005, about 604–795 million individuals suffered from Tricariasis, 0.807–1.221 billion suffered from ascariasis, and 576–740 million suffered from hookworm infections worldwide (Murat 2019). In 2019, intestinal infections due to nematodes caused 2090 deaths and 1.97 million DALYs (*Global Health Metrics* n.d.).

In 2015, the disease leishmaniasis was widespread in 88 subtropical, tropical, and temperate countries, with more than 350 million people at risk of exposure. An estimated 12 million patients suffer from leishmaniasis, with 0.2–0.4 million new visceral leishmaniasis (VL) and 0.7–1.2 million new cases of cutaneous leishmaniasis (CL) per year worldwide. (Georgiadou et al. 2015). The total number of new cases fluctuates over time and is difficult to estimate. For CL, the estimated number of new cases per year ranges from about 700,000 to 1.2 million or more. For VL, the estimated number of new cases per year may have decreased to <100,000, but previous estimates ranged up to 400,000 or more cases. The leishmaniasis cases evaluated in the United States reflect immigration and travel patterns. For example, many cases of CL in U.S. civilian tourists have been acquired in general tourist destinations in Costa Rica (Cdc 2023).

Schistosomiasis ranks second only to malaria in terms of the number of cases. Globally, an estimated 779 million people are at risk, and more than 207 million people are infected with schistosomiasis worldwide. In addition to the health consequences, schistosomiasis is associated with an economic and social impact. In Sub-Saharan Africa (SSA), while control interventions are underway, schistosomiasis still contributes more than 90% of the global schistosomiasis load. Schistosomiasis causes the loss of approximately 4.5 million DALYs and 150,000–280,000 deaths annually in the region (Mnkugwe et al. 2020).

An estimated 199 million total individuals (95% of uncertainty intervals of 174–234 million) worldwide were infected with lymphatic filariasis in 2000, with the total for the WHO region ranging from 107 million (91–134 million) in the Southeast Asian region to 3.1 million (1.6–5.7 million) in the American region. In 2018, an estimated 51 million people (43–63 million) were infected. A widespread decline in prevalence is observed globally. However, the attention of areas in Africa and Southeast Asia remains less, possibly due to reaching the threshold of the prevalence of infections for local elimination (Cromwell et al. 2020).

From Table 1, it can be seen that intestinal nematodes (Ascariasis, Tricariasis, Hookworm) contribute to the highest cases worldwide. However, in terms of mortalities, they have a lower number of deaths compared to Schistosomiasis. Schistosomiasis has a higher risk of exposure compared to Leishmaniasis. Compared to intestinal nematodes and Schistosomiasis, Cryptosporidiosis has the highest DALYs. However, more research is required as DAYLs and the risk of exposure to other diseases is not well known.

3.2 Incidence of parasitic zoonotic diseases in Indonesia

The incidence of zoonotic parasitic diseases in Indonesia continues to increase. Some examples of such diseases are toxoplasmosis, taeniasis, cysticercosis, schistosomiasis, cryptosporidiosis, and filariasis (IPB University 2013).

The incidence of toxoplasmosis in various regions of Indonesia is diverse, with prevalence ranges reported as 2%–51% and 2%–63% of the population (Gandahusada 1991; Soekiman 2017). Based on regions, the prevalence of toxoplasmosis ranges from 69.14% in Yogyakarta to 3.1% in Bali (Chomel et al. 1993; Muflikhah et al. 2018). In Middle Java, North Sulawesi, Surabaya, South Kalimantan, and Makassar, the prevalence of toxoplasmosis is 62.5%, 58.5%, 58%, 9.7%–51%, and 32.6%, respectively (Durfee & Cross 1976; Houki *et al.* 2000; Polanunu *et al.* 2021;

Retmanasari et al. 2017). When blood donors in Jakarta were checked for toxoplasma antibodies, 60% were positive (Soekiman 2017). Meanwhile, in Bali, 35.9% of blood donations were detected as positive for toxoplasmosis (Triana 2015).

Taeniasis and cysticercosis can still be found in Indonesia, especially in the provinces of North Sumatra, Bali, and Papua with a prevalence range of 2%–48%. Those areas are endemic areas of taeniasis and cysticercosis in Indonesia. From 2002–2009, a survey of taeniasis and cysticercosis by the method of detection of mitochondrial DNA was carried out on 660 people and 80 of them were positive for *T.saginata* and *T.solium*. The study also found 12 cases of neurocysticercosis (Sandy 2014).

Schistosomiasis in Indonesia is only found in Central Sulawesi Province, namely the Poso Regency and Lindu Plateau, Napu Plateau and Bada Plateau, and Sigi Regency. The incidence of schistosomiasis infecting humans in 2018 ranged from 0% to 5.1%. The prevalence of schistosomiasis in animals ranges from 0% to 10%. Before 2018, the prevalence of schistosomiasis fluctuated. In 2011–2015, the incidence of schistosomiasis in Lindu ranged from 0.8–1.7% while in Napu it ranged from 0.35–1.9% (Anastasia et al. 2019). Cryptosporidiosis is the main cause of diarrhea in infants and young children. In children, 5%–15% of cases of diarrhea are caused by Cryptosporidium. As the prevalence of immunosuppressive diseases such as HIV/AIDS and tuberculosis increases in Indonesia, more research and funding into cryptosporidium prevention and control is required (Wijayanti 2017).

Until 2014, in Indonesia, there were more than 14 thousand people spread across various provinces of Indonesia suffering from clinical chronic filariasis (elephantiasis). In terms of epidemiology, more than 120 million people are at risk of filariasis. At the end of 2014, around 45% of districts in Indonesia (235/511) had endemic filariasis, and this number could increase because some districts were still reported. The prevalence of filariasis turned out to be increasing with evidence that there were 10,681 cases of filariasis in Indonesia in 2018 and in some of them, there were cases of death and changes in diagnosis after confirmation of chronic clinical signs reported in the previous year. Papua, East Nusa Tenggara, West Java, West Papua, and Aceh are the five provinces with the highest incidence of filariasis in Indonesia, while the Special Region of Yogyakarta is the province with the lowest incidence of filariasis, which is only three cases (Budijanto 2019).

As discussed above and shown in Table 2, Indonesia has a variable, but high prevalence of zoonotic parasitic diseases. The incidence, prevalence, and risk factors for these diseases require further research to provide more accurate data on the impact these diseases have on the Indonesian population.

Table 2. Cases of zoonotic parasitic disease in Indonesia.

Name of disease	Prevalence	Prevalence based on region	Cases	Risk of exposure	References
Toxoplasmosis	2–51% 2–63%	Middle Java 62.5%	–	–	20,21
		Yogyakarta 69.14%			22,23
		Makassar 32.6%			24
		North Sulawesi 58.5%			25
		South Kalimantan 9.7–51%			26
		Bali 3.1%			27
		Surabaya 58%			28
Taeniasis and cysticercosis	2–48%		–	–	29
Schistosomiasis	0–5.1%		–	–	30
Cryptosporidiosis	5–15% of children's diarrhea		–	–	31
Filariasis	–		14 thousand	>120 million	32

3.3 Incidence of zoonotic disease with soil as transmission media globally

An STH refers to a group of intestinal parasites, including the roundworm *Ascaris lumbricoides*, the hookworm species *Necator americanus* and *Ancylostoma spp.* (including *A. duodenale* and

A. ceylanicum), and the whipworm *Trichuris trichiura* (Brooker et al. 2006). STHs are the cause of zoonotic diseases in adults as well as children. Zoonotic diseases caused by STHs can affect the cognitive development and physical growth of an infected individual. Zoonotic diseases whose transmission media is soil are strongly influenced by several factors, including high levels of poverty, poor environmental hygiene, defecation in an open environment, and inadequate sanitation (Kretchy 2022). The STHs infections mostly occur in the tropical and subtropical regions of SSA, Asia, and the Americas, where warm humid environments, poor hygiene and sanitation, and limited access to safe water sources facilitate the helminths' survival (Brooker et al. 2006).

Table 3. Cases of STHs globally.

Name of parasite	Cases (2003)	Cases (2010)	References
<i>A. lumbricoides</i>	1.2 billion	819 million	35,36
<i>T. trichiura</i>	795 million	464 million	35,36
hookworm	740 million	439 million	35,36

There are 1.7 billion people infected with STHs worldwide. According to a 2003 survey, there are more than 1.2 billion cases of *A. lumbricoides* in the world, of which more than half occur in China (Table 3). There are 795 million *T. trichiura* cases, whereas there are 740 million hookworm cases (De Silva *et al.* 2003). In 2010, Pullan et al. found that 819 million cases of *A. lumbricoides*, 464 million cases of *T. trichiura*, and 439 million cases of hookworm were found in South Asia and SSA. Many factors can explain this disparity, such as using only data from the global atlas of helminthic infections in the 2010 review and assessing only the population at risk and not the entire general population as a whole. Asia contributes 67% of the global prevalence of STHs; the highest prevalence is in India (21%) followed by China (18%) (Pullan et al. 2014). From Table 3, it can be derived that *A. lumbricoides* contributes the most cases compared to other STHs. The number of all STHs cases decreased possibly due to better living conditions and anthelmintic use (Pullan et al. 2014). However, this needs updated data as the latest data obtained was from more than 10 years ago.

3.4 Incidence of zoonotic disease with soil as transmission media in Indonesia

In Indonesia, STHs infections are endemic. In many areas of Indonesia, the environment, social and economic conditions are ideal for STHs infection. There are approximately 200 million people at risk of contracting STHs in 31 provinces (Gulati & Khatri 2009).

Table 4. Cases of STHs in Indonesia.

Name of parasite	Prevalence	Prevalence based on region	References	
<i>A. lumbricoides</i>	14%–90%	Sumatra 78%	38,39	
		Kalimantan 79%	38	
		Sulawesi 88%	38	
		West Nusa Tenggara 84%	38	
		West Java 91%	38	
<i>T. trichiura</i>	1%–91%	–	38	
		hookworm	21%–89%	38,39
			30%–50%	

According to parasitological surveys carried out in the 1980s and 1990s, the prevalence of *A. lumbricoides*, *T. trichiura*, and hookworm was between 14%–90%, 1–91%, and 21–89%, respectively (Gulati & Khatri 2009). STHs prevalence in Semarang, Central Java, was 20%–50%, (Pullan 1998) but these estimates are based on data that are more than a decade old.

In Indonesia, the prevalence of STHs infection is generally still high, especially in the populations with poor sanitation, with data varying from 2.5% to 62%, and the highest intensity was found among preschool and school children (Noviastuti 2015). Some surveys in Indonesia showed that often the high prevalence of *A. lumbricoides* was accompanied by the prevalence of *T. trichiura*. Prevalence of *A. lumbricoides* higher than 70% was found in Kalimantan (79%), Sumatra (78%), Sulawesi (88%), West Nusa Tenggara (92%) and West Java (90%). Prevalence of *T. trichiura* also high for the Sumatra (83%), Kalimantan (83%), Sulawesi (83%), West Nusa Tenggara (84%) and West Java (91%). Meanwhile, the prevalence of hookworms is around 30–50% in various regions in Indonesia (Novianty et al. 2018). Almost in all parts of Indonesia except Papua and Maluku, the prevalence of hookworm cases is high. The high range of prevalence between parasites may be due to the economic status, occupational status as farmers, and overcrowding of households (Kurscheid et al. 2020). *T. trichiura* and hookworm prevalence based on the region in Indonesia needs further research as no data was available.

4 CONCLUSION

There are primarily STH infections in the tropical and subtropical regions of SSA, Asia, and the Americas, where environmental humidity, poor hygiene and sanitation, and limited access to water facilitate helminth survival. In many areas of Indonesia, the environmental and socio-economic conditions support STH infections. This needs attention for better health education for practices related to hygiene and sanitation for the prevention of parasitic zoonotic cases in Indonesia and worldwide.

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The effectiveness of behavioral training ‘SENYUM’ for parents and teachers in maintaining dental-oral health among students with down syndrome

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ABSTRACT: Providing training for parents and teachers about how to brush teeth correctly and adequately can prevent caries and maintain dental-oral health among students with Down syndrome. Therefore, this study aimed to analyze the effectiveness of behavioral training ‘SENYUM’ provided to parents and teachers in maintaining dental-oral health among students with Down syndrome. This study used a *one-group pre-and post-test* design. The samples were 30 people, which included 15 teachers and 15 parents of students with Down syndrome. The sampling was purposively taken from homeroom teachers and parents of Down syndrome students who live with their children daily. Parents and teachers fill out a behavioral questionnaire before (pretest) and after (post-test) the behavioral training ‘SENYUM.’ The normally distributed data obtained were analyzed using a Paired T-test and Wilcoxon. There was a significant difference between the pre-test and post-test in a total of parent and teacher’s behavior ($p = <0.001$), indicating that the behavioral training ‘SENYUM’ has a significant effect on increasing parents’ and teachers’ total oral dental health behavior. The behavioral training ‘SENYUM’ effectively improves the dental-oral health behavior of parents and teachers in maintaining dental-oral health among students with Down syndrome.

1 INTRODUCTION

Dental-oral health impacts general well-being since it can reduce physical fitness and performance (Bramantoro *et al.* 2020). Many parents in Indonesia were unaware of the significance of dental care, particularly pediatric dental care. Parents will only seek pediatric dental care if their kids have dental issues (Zuhdi *et al.* 2020). Dental-oral health behavior is a critical component in maintaining dental-oral health (Katili *et al.* 2022).

The health promotion behavioral change theory underpins the dental-oral health behavior intervention (Pradhan *et al.* 2020). Several previous studies suggested behavioral interventions for maintaining the dental-oral health in children (Choi & Ahn 2012; Zuhdi *et al.*

2020). Nevertheless, this similar intervention still lacks in Down syndrome. The latest available studies in Down syndrome also did not involve both parents and teachers (Putri *et al.* 2018; Rizal *et al.*, 2019). Moreover, Down syndrome students had more challenges maintaining dental-oral health than regular students. The cognitive level in this population requires more effort to teach a new habit (Finlayson *et al.* 2019). A research conducted in Sweden by Stensson *et al.* (2020) shows that parental assistance is necessary to maintain oral dental health in Down syndrome. Teachers' values, beliefs, and attitudes strongly influence planned teaching outcomes for students with Down syndrome. The involvement of parents and teachers as role models in behavioral change in children, especially Down syndrome students, is required to achieve the desired results (McFadden *et al.* 2017). Therefore, this study plans to design a novel health behavior intervention for parents and teachers to maintain the dental-oral health of Down syndrome students.

2 METHODS

This one-group pre-and post-test study involved 15 parents and 15 teachers of Down syndrome students. The sampling technique was purposive with the following inclusive criteria: 1) Down syndrome students with mild intellectual disability who live with their parents; 2) Down syndrome students with mild intellectual disability aged ≥ 6 years old; 3) Homeroom teacher and school public health teacher of Down syndrome students with mild intellectual disability; 4) One of the parents whose a more intimate relationship with their own Down syndrome child, either the father or the mother; 5) Willing to be a participant.

The participants did the pre-test to measure their level of dental-oral behavior in maintaining the dental-oral health of Down syndrome students before the behavioral training 'SENYUM' was done. The behavioral training 'SENYUM' consists of delivering the 'SENYUM' module about dental-oral health behavior and guiding how to use the 'SENYUM' card to maintain the dental-oral health of Down syndrome students. The 'SENYUM' card is a picture card containing a checklist for monitoring and correcting oral health maintenance actions for students with Down syndrome. Parents and teachers will use this card to monitor and correct oral health maintenance actions for Down syndrome students with the 'SMILE' module guide. 'SENYUM' is an acronym that represents six groups of checklists for monitoring and maintaining the dental-oral health of Down syndrome students (Table 1).

Table 1. Behavioral training 'SENYUM' acronym description.

Acronym	Description
S	<i>Sikat gigi dengan benar dan tepat waktu</i> (Brush your teeth properly and on time)
E	<i>Evaluasi konsumsi makanan dan minuman manis</i> (Evaluation of of sweet foods and drinks' consumption)
N	<i>Nilai kondisi rongga mulut</i> (Assess the condition of the oral cavity)
Y	<i>Yuk periksa ke fasilitas pelayanan kesehatan gigi mulut (fasyankesgilit)</i> (Come and check out the oral dental health facility)
U	<i>Upayakan ganti sikat gigi tiap 3 bulan (segera setelah bulu sikat gigi rusak)</i> (Try to change your toothbrush every 3 months (as soon as the toothbrush bristles wear out))
M	<i>Makan buah dan sayur</i> (Eat fruits and vegetables)

The participants did the post-test to measure their level of dental-oral behavior in maintaining the dental-oral health of Down syndrome students after the behavioral training ‘SENYUM’ was done. The pre-test and post-test evaluate the knowledge (20 items), attitude (11 items), and action (10 items) in maintaining dental-oral health both in parents and teachers of Down syndrome students using a validated behavioral questionnaire. Data were further obtained as numerical ratio data and subsequently analyzed using Paired T-test and Wilcoxon test on IBM SPSS Statistics® 26.00.

3 RESULTS

There were 15 parents, with 3 (20%) male and 12 (80%) female, and an average age range of 39.27 ± 18.44 years. In addition, there were 15 teachers with 3 (20%) male and 12 (80%) female with an average age range of 44.73 ± 15.53 years.

3.1 Level of dental-oral behavior among parents and teachers

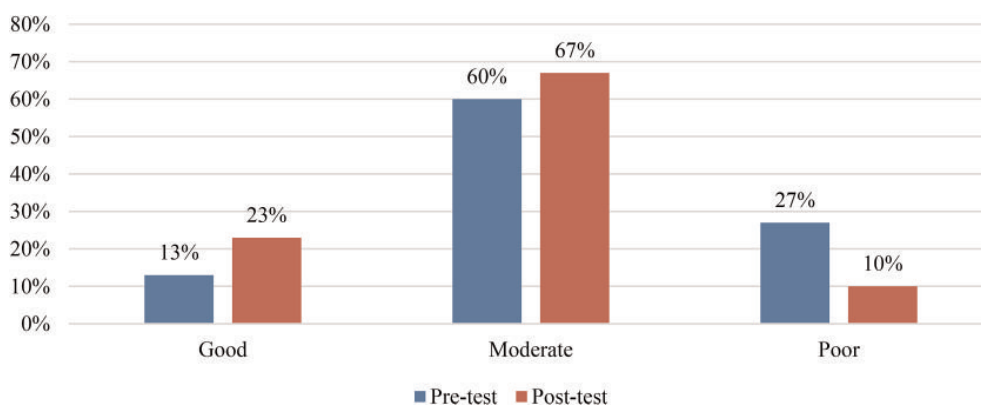


Figure 1. Level of dental-oral behavior among parents and teachers pre and post behavior training ‘SENYUM’.

Furthermore, this study measured the level of behavior which is come from total of components of knowledge, attitude, and action, which were categorized into good, moderate, and poor (Figure 1). There were an increase level of behavior both in good and moderate category after behavioral training ‘SENYUM’. Contrarily, there were a decrease level of behavior in poor category after behavioral training ‘SENYUM’. It was indicated that there was an improvement of behavior level to good and moderate category after behavioral training ‘SENYUM’.

3.2 Analysis of dental-oral behavior among parents and teachers

The level of dental-oral behavior among parents and teachers of Down syndrome students was further analyzed using a statistical test. There were significant differences in each of the components of dental-oral behavior (knowledge, attitude, action) between the pre-test and post-test from both parents ($p = 0,004$; $p = 0.011$; $p = 0.008$ respectively) and teachers ($p = 0.010$; $p = 0.005$; $p = <0.001$). The total score of behavior from both parents ($p < 001$) and teachers ($p < 0.001$) also showed significant differences. The total score from parents and teachers in the pre-test and post-test were also evaluated and appeared to be significant ($p < 0.001$) (Table 2). These results indicated that behavioral training ‘SENYUM’ significantly affects the dental-oral health behavior of parents and teachers in maintaining dental-oral health among students with Down syndrome.

Table 2. Differences between pre and post behavioral training ‘SENYUM’ among parents and teachers of down syndrome students.

Variable	Pre-test	Post-test	P-value
Parents’ Behavior			
Knowledge	11.67 ± 4.48	14.60 ± 3.50	0.004 ^a
Attitude	24.67 ± 4.51	26.47 ± 5.05	0.011 ^b
Action	16.80 ± 2.65	17.73 ± 3.41	0.008 ^a
Teachers’ Behavior			
Knowledge	15.80 ± 3.43	17.60 ± 3.04	0.010 ^b
Attitude	27.93 ± 3.51	29.27 ± 3.47	0.005 ^a
Action	18.80 ± 4.31	20.60 ± 4.37	<0.001 ^a
Total of Parents’ Behavior	53.13 ± 7.27	58.80 ± 5.76	<0.001 ^a
Total of Teachers’ Behavior	62.53 ± 9.18	67.47 ± 8.67	<0.001 ^a
Total of Parents’ and Teachers’ Behavior	57.83 ± 9.44	63.13 ± 8.47	<0.001 ^a

^aPaired T-test

^bWilcoxon Test

4 DISCUSSION

The behavioral training ‘SENYUM’ is aimed to parents and teachers who are role models for students with Down syndrome. According to the literature, role models have an important duty for students with Downs syndrome to have a good habit that supports their health (Ku *et al.* 2020; McFadden *et al.* 2017). Therefore, this study aimed to provide good and efficient training for parents and teachers to maintain children’s dental- oral health.

From the results of this study, it was discovered that parents and teachers of students with Down syndrome had dental-oral health behavior with the majority in the less-moderate category. This showed that parents and teachers have an awareness that dental-oral health is important but not optimal. Therefore, training is still needed to obtain maximum results (Choi & Ahn 2012; Scalioni *et al.* 2018).

Before this study was conducted, the pre-test showed that the oral health behavior of teachers was higher than parents. This is supported by Gomes *et al.* (2015), which stated that knowledge of oral health is significantly related to the level of education.

The results also showed that there was a significant increase in scores regarding the oral health behavior of parents and teachers ($p < 0.001$). This is in line with a previous report, where dental-oral health training significantly improved oral health behavior (Amin *et al.* 2014; Catteau *et al.* 2016; Khurana *et al.* 2020).

The behavioral components containing knowledge, attitude, and action had a significant increase ($p < 0.05$) after being given training. Similarly, it was discovered that the components have an interrelated and directly proportional relationship with dental-oral health habits (Akbar *et al.* 2017; Tolvanen *et al.* 2012). The limitation of this study is the number of samples that can be increased. Therefore, further investigation with a larger number of samples can strengthen the results obtained.

5 CONCLUSION

Behavioral training ‘SENYUM’ was significantly effective in improving the behavior of parents and teachers in maintaining the oral health of students with Down syndrome.

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The prevalence of hypertension, diabetes mellitus and tuberculosis comorbidities in Indonesia

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ABSTRACT: The comorbidities of hypertension, diabetes mellitus (DM) and tuberculosis (TB) are significant burden on the health system. This study aims to determine the prevalence of hypertension, DM and TB comorbidities in Indonesia. We included 30,088 adults (aged >18 years) from the 2014 Indonesian Family Life Survey (IFLS) 5. TB diagnosis was self-reported, while the diagnosis of hypertension and DM were either self-reported or measured (blood pressure $\geq 140/90$ mmHg; A1c ≥ 6.5 mg/dl). Descriptive analysis was conducted using STATA 16.0. Half respondents were female (52.8%), aged between 24–44 years old (45.6%), from urban areas (52%), never smoke (61.6%) and had normal BMI (39.6%). TB-DM comorbidity was 0.1% (95%CI 0.06–.15), DM-hypertension comorbidity 3.77% (95%CI 3.49–4.08), and TB-hypertension comorbidity 0.35% (95% CI 0.28–0.44). The prevalence of comorbidities of the three diseases is low, however screening of these conditions is essential to improve early diagnosis and treatment.

1 INTRODUCTION

Non-communicable diseases (NCDs) are still a global health burden, killing 41 million people each year, which accounted for 74% of global deaths in 2012 (WHO 2021). Every two seconds, one person dies prematurely from NCDs, and more than 85% of deaths take place in low- and middle-income nations (LMICs). The high prevalence of NCDs contributes to poverty, impedes economic growth, and strains the healthcare system (CDC 2021). The leading causes of NCD-related death include cardiovascular disease, chronic respiratory disease, cancer, and diabetes mellitus (DM) (WHO 2021). The most prevalent metabolic risk factors for NCDs are type 2 diabetes and hypertension (Uthman *et al.* 2022).

The global health burden of DM is still high. Diabetes will be responsible for 6.7 million fatalities in 2021, and more than three out of every four persons with diabetes live in high-income nations (Wang *et al.* 2022). Indonesia is ranked seventh in terms of the most prevalent DM cases, with 10.7 million people affected (RI 2020). One in nine Indonesians suffers from diabetes. Diabetes was responsible for 236,711 deaths in Indonesia (Federation 2022).

Diabetes patients frequently have multimorbidity (two or more chronic illnesses), which will affect 60% of patients by 2032. Previous research found that the presence of multimorbidity was associated with increased mortality and disability, increased polypharmacy, lower function level, decreased health-related quality of life (HRQoL), and increased healthcare burden (cost, number of doctor visits, length of hospital stay) (Huntley *et al.* 2012;

Husnayain *et al.* 2020; Rodrigues *et al.* 2021; Walker *et al.* 2016). Case finding and early detection of multimorbidity simultaneously and comprehensively are needed to decrease mortality and disability (Mercer *et al.* 2016).

Hypertension (37%), and ischemic heart disease (10%) were the most common comorbidities discovered. This prevalence increases along with the disease course (Pearson-Stuttard *et al.* 2022). Diabetes was found to be substantially related with hypertension in an Indonesian investigation. Diabetes in the elderly (60–74 years old) was 2.32 times more likely than in the elderly without diabetes. (Oktaviyani *et al.* 2022). In addition, DM increases the risk of developing tuberculosis (TB), and vice versa. In 2019, just over 15% of people with TB were estimated to have diabetes globally, and in 2020, 370,000 new cases of TB were attributable to diabetes. This incidence is increasing in TB-endemic countries (WHO 2021).

Indonesia has a high prevalence of tuberculosis and diabetes. 13.2% of tuberculosis patients have diabetes (Alisjahbana *et al.* 2006). A study on TB and NCD multimorbidity reported that the prevalence of TB is increasing in line with the increase in NCD cases. Good management of TB and NCDs can provide better outcomes (Stubbs *et al.* 2021; Ugarte-Gil *et al.* 2020). There is currently little knowledge available regarding the prevalence of comorbidity among these three illnesses. The objective of this study is to find out how common concomitant TB, DM, and hypertension are in Indonesia.

2 METHODS

We made use of secondary data from the 2014–2015 Indonesian Family Life Survey (IFLS5). In Indonesia, The IFLS is a long-term survey. The sample includes almost 30,000 people from 13 of Indonesia's 27 provinces, representing approximately 83% of the Indonesian population. This survey collects information about individual respondents, their neighborhood, their households, their families, and the health and education facilities they utilize.

Inclusion criteria were individuals aged ≥ 18 years. Tuberculosis was self-reported by the respondents. Hypertension and DM were either self-reported or measured (blood pressure $\geq 140/90$ mmHg; A1c ≥ 6.5 mg/dl). Observational data with implausible biological values or incomplete data were excluded from the analysis.

We included respondent variables that could be confounding factors, such as age, gender, smoking status, body mass index (BMI), and degree of education. Furthermore, the region of habitation, ventilation, and household member were all incorporated. According to Ministry of Health criteria, age was classified as follows: youth (15–24 years old), adult (25–44 years old), pre-elderly (45–59 years old), and elderly (60 years old). BMI was measured using structured questionnaires and divided into four groups based on Indonesian Ministry of Health guidelines: underweight (BMI 18.5 kg/m^2), normal (BMI $18.5\text{--}22.9 \text{ kg/m}^2$), overweight (BMI $23\text{--}24.9 \text{ kg/m}^2$), and obese (BMI 25 kg/m^2). We did a descriptive statistical analysis using STATA 16.0.

3 RESULTS

30,088 respondents made up the study's sample size. Women (52.82%) predominated more than men (47.18%) in the age range of 25 to 44 years, while the majority of individuals (45.62%) were female. Both senior high school (44.44%) and elementary school (43.62%) have nearly identical educational levels. The majority of respondents (61.64%) did not smoke, and 39.60% of them had a BMI of normal weight. The majority of respondents (51.99%) reside in urban areas with good ventilation (85.57%) and fewer than two family members (50.85%) (Table 1).

Table 1. Sociodemographic characteristics of the respondents.

Characteristics	Proportion n = 30088 Weighted % (SE)
Age	
18–24	13.07 (0.20)
25–44	45.62 (0.32)
45–59	27.31 (0.31)
>60	13.99 (0.24)
Sex*	
Female	52.82 (0.33)
Male	47.18 (0.33)
Education	
Primary school or less	43.62 (0.33)
High school	44.44 (0.32)
University	11.94 (0.20)
Smoking Status*	
Never smokers	61.64 (0.32)
Current smokers	33.24 (0.31)
Past smokers	5.12 (0.14)
BMI status*	
Underweight	11.07 (0.21)
Normo-weight	39.60 (0.32)
Overweight	16.01 (0.24)
Obesity	33.31 (0.31)
Area of residence*	
Rural	48.01 (0.33)
Urban	51.99 (0.33)
Ventilation	
Not adequate ventilation	14.43 (0.23)
Adequate ventilation	85.57 (0.23)
Household members	
<=2	50.85 (0.33)
3–4	38.62 (0.32)
>=5	10.53 (0.2)

Note: *) shows significant result of $p < 0.05$

The prevalence of TB and DM comorbidity was 0.1% (95%CI 0.06%–0.15%). The prevalence of diabetes and hypertension comorbidity was 3.77% (95%CI 3.49%–4.08%). The prevalence of TB-hypertension comorbidity was 0.35% (95%CI 0.28%–0.44%) (Table 2).

Table 2. The prevalence hypertension, TB, diabetes comorbidities.

Variables	Prevalence (CI 95%)
TB- DM	0.1 (0.06, 0.15)
TB-HT	0.35 (0.28, 0.44)
DM-HT	3.77 (3.49, 4.08)

Note: Data are presented as proportion (95% ci)

4 DISCUSSION

The Collaborative Framework for Care and Control of Tuberculosis and Diabetes was published by WHO in 2011 as a result of the comorbidity of diabetes and tuberculosis (DM-TB) becoming a major public health issue globally, particularly in settings with limited resources and in nations with a high TB burden. In 2019, it was predicted that among all individuals (20–79 years old), more than 15% of those with TB also had diabetes (WHO 2021). Determining the prevalence of TB-DM comorbidities could potentially push programmed and policymakers to take effective action.

It was more difficult to manage TB patients who also had diabetes (Behzadmehr & Rezaie-Keikhaie 2022). According to one study, TB patients with diabetes showed more severe clinical symptoms, delayed sputum conversion, and a higher risk of treatment failure and recurrence rates (Gautam *et al.* 2021; Jiménez-Corona *et al.* 2013; Yoon *et al.* 2017). Once infected, those with diabetes have a three times higher risk of developing active TB (Al-Rifai *et al.* 2017). Poor glycemic management, dyslipidemia, and a chronic inflammatory response all lead to an immunological dysfunction condition that affects the body's defense and lowers phagocytic ability in response to *M. tuberculosis* (Eckold *et al.* 2021).

A previous study in Jakarta showed that TB-DM case detection increased significantly in 2019 compared to 2017 and 2018 (Jiang *et al.* 2022). According to a systematic review, the prevalence of DM ranged from 1.9% to 45% among tuberculosis patients, and the prevalence of TB among DM patients ranged from 0.38% to 14% (Workneh *et al.* 2017).

It is still unclear how TB and hypertension are related. According to a study, TB patients were more likely to have hypertension at the time of diagnosis (38.7% vs. 37.5%, $p = 0.03$) (Chung *et al.* 2014). However, a comprehensive analysis found no evidence to indicate a connection between hypertension and tuberculosis (Borchsenius *et al.* 2017).

TB can cause hypertension through cell destruction in parenchymal cells in the lung tissue. The disruption will cause constriction of the blood vessels around it and cause pulmonary hypertension. When TB infects the kidney, reducing kidney function and weakening the ability to regulate the blood pressure. These can cause hypertension (Satria & Riono 2018). Elevated levels of interleukin, NADPH oxidase, and ROS may increase the higher risk of infection-related death in hypertensive people. Hypertension was discovered to be a trustworthy predictor of both all-cause and infection-related death within the first nine months after beginning TB medication (Chidambaram *et al.* 2021).

Hypertension and DM are chronic diseases that occur concurrently. Their confluence has a significant role in the development and progression of microvascular and macrovascular problems. Hypertension was shown to be prevalent in 37.4% of diabetes patients. (Abdissa & Kene 2020). A study in Indonesia reported that the prevalence of hypertension among diabetic patients was 17.5% (Azam *et al.* 2020).

The results of these three prevalence's in this study were lower than in previous studies. The limitation of this study is the high risk of bias because the diagnosis is based on self-reported. It could have led to an underestimation or overestimation of this prevalence estimate.

The prevalence of comorbidities such as hypertension, diabetes, and tuberculosis has been determined in this study; however, more research is required to determine the ideal period for screening as well as to find a reliable and affordable technique. These three diseases can be less burdensome if they are detected early and case discovery is improved.

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The barriers to prevent smoking behavior of junior high school students: A qualitative study

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ABSTRACT: Prevention of adolescent smoking behavior is no progress. This condition is the impact of failure in defining barriers in this activity. This study aims to explore the barriers to preventing early adolescent smoking behavior. This study used a qualitative method for 52 selected participants (junior high school students, parents of students, religious leaders, community leaders, representatives of the Office of Health, and representatives of the Office of Education). The researchers carried out data collection using semi-structured interviews. From the interviews, the researchers identified the barriers to the prevention of early adolescent smoking behavior from various perspectives. The researchers divided research results into internal barriers and external barriers. Internal barriers are in the form of attitudes toward smoking behavior and low motivation to not smoke. External barriers are ease of access to cigarettes, lack of parental participation, influence from strong peers, and socio-culture. Barriers to the prevention of smoking behavior spread in various aspects. Identifying its factors that can overcome barriers to preventing smoking behavior in early adolescence. This information can optimize the preparation of health education to adolescents to prevent their smoking behavior.

1 INTRODUCTION

Teenage smoking behavior is influenced by many factors. Adolescents smoke because of friendship (Mpousiou *et al.* 2018). Peers become a reference group for early adolescents (Robalino & Macy 2018). Adolescents have a potent influence on the development of early adolescent smoking behavior (Kumboyo *et al.* 2020). Adolescent smoking behavior is also associated with a lack of knowledge of the negative impact of smoking on health (Lim *et al.* 2019). The adolescents assume they are young, so the negative effects of the cigarettes will not affect them. Furthermore, it relates to parental behavior. Most early adolescents who smoke have parents or relatives who smoke (Cheney & Mansker 2014). Parents are the initial models for shaping children's behavior. Often the society's norm system also has a big influence in shaping this behavior. An apathetic society tends to make it easier for teenagers to smoke (Kumboyo *et al.* 2020).

In Indonesia, the prevalence of smoking among adolescents between the ages of 10–18 is increasing. Basic health study findings in 2018 found that teen smokers aged 10–18 years had increased by 1.9 percent over five years. In 2013, the prevalence of adolescent smoking in Indonesia was 7.2 percent and increased to 8.8 percent in 2016 and 9.1 percent in 2018 (Balitbang Kemenkes Republik Indonesia 2018).

The growing number of teen smokers is not because no attempt is made to avoid it. Various interventions to solve the smoking prevalence are introduced with various strategies.

Public regulations on the sale and promotion of cigarettes are made using behavior change communication, for example. It is an intervention to make sustainable changes to public health behavior. Contact focuses on the cycle of understanding and encourages people to have healthy habits that promote a better state of health (Schiavo 2013).

Health promotion was carried out by various parties through different platforms, including face-to-face and the media. Health contact performed to influence smoking activity in youth, however, is still not having any major effect. These various preventive efforts start from the National to the regional levels (Nurwidya *et al.* 2014). The government has adopted the MPOWER program that has been issued by the WHO. In 2013, the central government issued regulations regulating advertisements and sponsorship from cigarette companies. Furthermore, through the same regulations, the government also encourages regional regulations to regulate smoking-free areas. This program prohibits the sale of cigarettes and smoking in public spaces, one of which is school (Peta Jalan Pengendalian Dampak Konsumsi Rokok Bagi Kesehatan 2013). Besides, the government has also launched a Community Movement for Healthy Living (GERMAS) program in 2016.

Following multiple attempts to discourage smoking activity in early teens, no substantial reduction was observed (Septiono *et al.* 2019). Failure to minimize early teen smokers is due to challenges from different groups. To discourage early adolescent smoking behavior, the researchers conducted this study to summarize some barriers that exist in the area. The methodological approach was used to investigate barriers to avoidance of smoking activity in early adolescents.

Most of the previous studies focused on analyzing barriers to helping adolescents quit smoking. There are still fewer studies that explore qualitative barriers to preventing smoking behavior in adolescents (Chean *et al.* 2019). Due to the limited number of qualitative studies that examine the barriers that occur in preventing early adolescents from smoking comprehensively, this study aims to complement the study of the prevention of smoking behavior in early adolescents qualitatively. Therefore, the study aims to explore the various barriers to preventing smoking behavior in early adolescents from the perpetrators' point of view.

2 RESEARCH METHOD

The researchers conducted this research in Tegal City, Central Java Province, Indonesia. The study period was October-December in 2019. The study was focused on junior high students because the prevalence of adolescent smokers in Tegal City is relatively high. Research conducted by the Tegal City Health Office in 2014 showed that 33.61 percent of 123 junior high school students smoked (Dinkes Kota Tegal 2015).

The researchers compiled this guideline based on theories from previous references (Seidman & G 2006). The guidance questions were divided into two parts: one for students and the other for stakeholders. When required, probes and follow-up questions were added during the interview process to facilitate elaboration and clarification of answers. Specific questions were introduced as the method of interviewing concepts evolved in response.

The participants in this study came from some elements, which were divided into junior high school students, parents of students, junior high school teachers, religious leaders, community leaders, representatives of the education office, and representatives of the health office. The students who became the focus of the study were male junior school students who had experience dealing with cigarettes. The recruitment of participants from other parties was based on their central roles in the prevention of adolescent smoking behavior and was partly developed from the previous participants (in this study: snowball sampling). At the start of the study, we did not determine the number of participants. The number of participants is determined based on saturation data. This is by the principles of qualitative research so that data is collected simultaneously (Miles *et al.* 2019).

Protocol for this study was approved by the Ethics Committee for Health Research of Sebelas Maret University Surakarta, Indonesia (registration number 344/ UNS27.06 /KEPK /EC/2019). The goals of the study were explained to the participants, and after giving informed consent they decided to voluntarily participate in the study. Data confidentiality was maintained at all stages of the analysis, and results were reported as aggregated rather than individual individuals. Every of the information collected was kept confidential and only used for academic purposes.

3 RESULTS

The researchers divided early adolescent research into barriers to prevention in two main topics: internal and external. Internal barriers are that of the students, while external barriers are beyond learning barriers. Then, the researchers built two topics into seven more comprehensive topics.

3.1 *Theme 1: Attitudes of teenagers to smoking*

Most young people have a low smoking attitude. Some young people are still smoking although they are unhealthy. The finding of the following extract from the interview shows this:

- When I smoke, my chest is tight, but I keep smoking because it is tasty (Teenager 12).

Another opinion is an attitude that does not believe that smoking can kill. Teenagers of this opinion think that life or death is God's destiny. This attitude is expressed in the following interview passage:

- I know cigarettes can kill me. But I do not believe that, for to me life and death are in the hands of God (Teenager 14).

Some teenagers are even more assertive that they will not stop smoking even though they have known the danger of smoking to health. This attitude appears in their statement:

- I do not believe cigarettes can kill. I do not want to stop smoking and don't want to stop (Teenager 20).

3.2 *Theme 2: The motivation of adolescents to not smoke*

Some students experience health problems when they smoke, but they find it difficult to stop smoking because their friends smoke, so in brief, these students do not want to stop smoking. They express this experience in following transcripts:

- I was hospitalized for 2 days, the doctor forbids me to smoke, I am afraid of being relapsed if I am smoking, but it is hard to avoid smoking when together with friends (Teenager 6).
- My asthma has recurred because I smoke, but my friend provoked me to smoke continuously. I often smoke when I play games with my friend. Now I try to stop, but it is so hard (Teenager 24).

Another experience is that these students can not stop it, so they struggle to reduce the frequency of smoking, as stated below:

- I have once tried to stop smoking because my chest is tight, but I can not stop smoking. Sometimes, I reduce smoking frequently. Now, I smoke if there is a problem (Teenager 11).

3.3 *Theme 3: Ease of access to cigarettes*

A significant barrier in preventing the smoking behavior of junior high school students is the access to cigarettes. Many stalls sell cigarettes to teenagers and the price of cigarettes can be affordable. Many stalls around the school sell cigarettes at retail (per stick). The participants reveal this in the following interview excerpt.

- I sometimes buy cigarette bars by setting aside my allowance (Teenager 14).
- I buy it in a stall if there is no money to buy bars (Teenagers 15).

Adolescent access to cigarettes sometimes comes from home. Some parents give cigarettes to their children. The following participants stated this:

- I once smoked with parents, I asked for a cigarette from the father and was given (Teenager 9).
- I once took a parent's cigarette because my parents put the cigarette on the table (Teenager 27)

3.4 *Theme 4: Low parental assistance*

Barriers arise in the home environment due to the parents' less time to spend for their the children at home with the excuse of busyness. The participants revealed this in the following interview:

- I hope parents often sit together at home. Most parents rarely gather with family, just to chat (Health Office Representative).
- My parents never talked about smoking before they knew I was smoking (Teenager 6).
- Another barrier is the permission from parents to smoke when the children are adults. The following participants revealed this:
- I can not smoke because I am still a child, but if I am already working, they allow me to smoke (Teenager 7).
- When I grow up, I may smoke (Teenager 8).

The last barrier is the parents' smoking behavior at home. Many parents smoke carelessly at home. This indirectly provides a poor example for teens. The following participants revealed this condition:

- My parent often smokes when at home, he puts it on the table, and he asks me to buy cigarettes (Teenager 20).
- My parents and brother smoke at home. Sometimes I am asked to help buy cigarettes in a stall (Teenager 21).

3.5 *Theme 5: Strong peer impact*

Peers are a powerful factor influencing the formation of behavior in adolescents. Most of the student smoking behavior is because of friendship, as revealed in the following interview:

- My older friend asked me to smoke in the 4th grade (Teenager 20).
- My friend offered me in grade 5 elementary school. I refused, but a friend forced me (Teenager 26).

Peer influence is stronger when the participants gather. They claim it is difficult to avoid this behavior at the moment, as expressed by the participants in the following statement:

- I once tried to quit smoking but I could not because my friends always offered me cigarettes (Teenager 4).
- I once tried to quit smoking when not playing with friends, but often failed because friends asked me to smoke (Teenager 10).

3.6 Theme 6: Lack of teacher understanding

Barriers to the prevention of smoking behavior in the school environment are that there are still many teachers who smoke at school. Several participants from the teachers revealed this condition in the following interview excerpt:

- There are still one or two teachers who smoke in the school environment (Teacher 1).
- Here, one obstacle is teachers who smoke, even the principal of school smokes. Several times, students look at them smoking in the school environment (Teacher 7).

Another barrier in schools is that schools cannot control the smoking behavior outside the school environment. Schools do not have responsibilities related to student behavior when these students are out of school. The behavior outside of school is the responsibility of the parents, as stated by the following participants:

- There have been reports of children smoking in stalls around the school. It also happened outside of school hours, although still wear school uniforms. We need evidence to create the summons (Teacher 2).

3.7 Theme 7: Community attitudes toward teen smokers

Most people are apathetic with student smoking behavior. They prefer silence when they see school children who are still wearing school uniforms smoking. They revealed this in the opinion of the following participants:

- Many children still use smoking uniforms on the side of the road. But no one rebuked (Teacher 6).

Some people do not want to reprimand smoking students because they do not know these students. They will just rebuke the proven one, as the following participants put it:

- I have never rebuked teenagers who smoke on the street. I only advise teens who are my responsibility (Religious Leader 1).
- I advise teenagers only in school where I teach. I did not consciously counsel teenagers extensively (Community Leader 1).

There are even some people who do not care and protect students who smoke in case of raids from schools. The attitude of the community assesses that school students smoking is common and not a big problem. The following participants expressed this:

- People around here are mostly ignorant when they see children smoking. They even sometimes like to protect when there are raids from school (Teacher 7).

4 DISCUSSION

Research by Kumboyono *et al.* has shown that barriers to smoking behavior prevention in early adolescents in school are closely related to parents, teachers, and peers (Kumboyono *et al.* 2018). Meanwhile, Rozema's research results indicate that the failure of adolescent smoking prevention activities is related to socio-political characteristics, school characteristics, individual characteristics and smoking ban characteristics (Rozema *et al.* 2016). This current study adds to what has been studied in previous studies. The area of this research does not only examine barriers to preventing outside smoking behavior of the perpetrators. The researchers discuss the barriers to preventing the smoking behavior of adolescents from two sides, namely from the youth side and from the stakeholder and community side. Besides, the uniqueness of this research is that it uses the grounded theory method. The

results of the study resulted in a direct experience of barriers to smoking prevention, which then formed a theory that explained the barriers to preventing teenage smoking.

The first major theme that emerged was low attitudes and motivation in adolescents. The results of this study are in line with strengthening the results of the quantitative research that has been conducted, which shows that adolescents who smoke have positive attitudes and motivations towards smoking (Xu *et al.* 2016). This theme is related to the theme of the strong influence of peers who smoke. It also reinforces the findings that friends have an important position in the formation of adolescents (Mpousiou *et al.* 2018; Pandayu *et al.* 2017). Most teenagers can avoid smoking if they don't hang out with their playmates.

Furthermore, the internal theme is related to the low level of parental and teacher guidance. Parents and teachers are the figures responsible for educating the adolescents. Parents are the first model for their children, while teachers are tasked with educating adolescents formally. Their role is very central in shaping adolescent behavior. Unfortunately, the research findings found the opposite. Many parents and teachers are not the role models for these adolescents regarding smoking behavior. They often smoke in front of their children and cannot limit themselves to smoking (Gercek 2018; Susanto *et al.* 2020). This is a bad percentage for the prevention of smoking behavior. The parents are positively supposed to be the driving force behind adolescent avoidance of smoking (Susanto *et al.* 2020).

The theme of easy access to cigarettes is closely related to special programs to prevent smoking in adolescents and weak enforcement of regulations. Smoking behavior prevention needs a strong regulatory support. Weak enforcement of regulations gives adolescents access to smoking (Rukmi 2019). This has led to a tendency to consider smoking a very common thing. The impact is that there is an opinion that the smoking prevention program is an urgent matter. This study suggests that the government conducts a field survey, so that it knows that a comprehensive and specific adolescent smoking behavior prevention plan is urgently needed (Pierce *et al.* 2012).

Next, the theme of apathetic society with the behavior of teenagers who smoke. This study confirms that the socio-culture in society has a significant effect on behavior prevention. The socio-cultural climate has a strong impact on the production of adolescent smoking behavior (Chean *et al.* 2019). Public attitudes that ignore early adolescent smoking hinder the prevention of adolescent smoking behavior. This attitude provides opportunities for adolescents to shape their smoking behavior.

5 CONCLUSION

Research findings consistently show that the prevention of adolescent smoking behavior is not a simple matter. It takes patience, effort, and partnership with all parties. Efforts to prevent adolescent smoking behavior from an early age must be started early at home. Schools must also continuously campaign for preventive action by involving students. Education for adolescents should not only emphasize short-term health risks but also emphasize other disadvantages of this behavior. Prevention of smoking behavior of early adolescents also requires programs and budget funds from the government to refine regulations and enforce community regulations. Failure to prevent smoking is due to the absence of cooperation from stakeholders. Each stakeholder tends to act independently. Besides, there are no competent figures who intensively guide parents and adolescent health education. This study provides information for health educators to identify various barriers in the preparation of health education and promotion plans to prevent adolescent smoking behavior. Exploring existing barriers can support solid health education planning. In the future, a sustainable smoking behavior prevention program that involves many parties is needed. Besides, health education activities should be not only at the individual level but also at the institutional level.

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The current and future direction in cognitive remediation therapy for mental disorders

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ABSTRACT: Cognitive deficits are a core feature of many severe mental disorders. Persistence of cognitive symptoms following standard treatments of mental disorders may indicate inadequacy of psychotropic medications in fully treating them. Consequently, persistence of cognitive deficits may itself have direct or indirect influence on treatment strategies and thus, limiting their efficacy. It may also be possible that prominence of cognitive deficits may have led to hindrances to effective execution of psychiatric rehabilitation programmes. Over the last two decades, cognitive remediation therapy (CRT) has been increasingly recognized as an evidence-based approach to ameliorate cognitive deficits in mental disorders. Several models of CRT have emerged since then, but the basic principles used are similar. Although much of the work in CRT has been focused on its application in the treatment of schizophrenia, the use of CRT has now been extended to other mental disorders including major depressive disorder, chronic neurocognitive disorders, traumatic brain injury, autism spectrum disorder, attention deficit hyperactivity disorder (ADHD) and eating disorders with some promising results. In addition to several computer-based CRT models, newer CRT models are being using cutting-edge technologies such as enhanced reality to boost the delivery and outcome of CRT in tandem with IR 4.0.

1 INTRODUCTION

The concept of “cognitive rehabilitation” probably emerged during WWI and WWII by Russians, Germans, and USA military service to rehabilitate soldiers who were cognitively impaired due to battlefield-related traumatic brain injury (Bontke & Boake 1991).

Luria was probably one of the earliest to look at cognitive rehabilitation with much interest (Luria 1963) and over the years his concepts of neurobehavioural treatment have been fundamental in the evolution of many cognitive rehabilitation methods in modern days (Rothi & Horner 1983). The first, the “restorative approach” or restitution of function is an approach which assumes that behavioral improvement results from the increasing integrity of the injured functional system through specific cognitive rehabilitative measures aiming to maximize the potentials of non-injured “brain reserves” to enable restoration of lost cognitive functions. In contrast, his concept of “adaptive approach” or substitution of function is a complementary approach that assumes improvement results from system reorganization or compensation. The assumption of this approach is to provide some sort of “psychological prosthesis” to compensate for the loss of cognitive function where restoration is no longer possible.

More recently, the interest in cognitive rehabilitation for schizophrenia and later for other major mental disorders emerged because cognitive deficits have been identified as major or core features of many mental disorders (Bajwa *et al.* 2019; Brockmeyer *et al.* 2016; McGurk *et al.* 2007; Twamley *et al.* 2003, 2011). People with schizophrenia, for instance, perform 0.8 to 1.5 standard deviations worse than control subjects in most neuropsychological tests (Fioravanti *et al.* 2012). The main deficits identified include deficits in attention and concentration, problem-solving, executive function, memory, and social cognition (Keefe *et al.* 2006). Similarly, various cognitive deficits have been identified as a prominent presentation in other mental disorders (Millan *et al.* 2012). A brief summary of the common cognitive deficits in these disorders is shown in Table 1. What is striking is that in all disorders, attention and memory deficits are invariably present.

Table 1. Cognitive deficits are a common feature in many mental disorders (Millan *et al.* 2012).

Psychiatric Disorder	Common Cognitive Deficits
Bipolar Disorder	<ul style="list-style-type: none"> ● Attention (response inhibition), verbal learning, executive functioning. ● Manic phase – sustained attention.
Major Depressive Disorder	<ul style="list-style-type: none"> ● Attention, response inhibition, verbal memory, executive function, cognitive flexibility.
Anxiety Disorders	<ul style="list-style-type: none"> ● Generalized Anxiety Disorder: Selective attention and working memory. ● Panic Disorder: Information processing, working memory, visual memory task. ● Post-Traumatic Stress Disorder: attention, working memory, planning, judgment. ● Obsessive Compulsive Disorder: Memory, attention, verbal fluency, organization, planning, spatial memory, motor speed
Childhood Disorders	<ul style="list-style-type: none"> ● Attention Deficit Hyperactive Disorder: Executive function, response inhibition, sustained attention, reaction time variability, verbal memory process deficit, verbal and nonverbal working memory deficit, visual motor integration, visual-spatial memory, and social cognition. ● Autism Spectrum Disorder: Cognitive flexibility, attention, social cognition—communication, social interaction, memory recall, verbal fluency, processing speed.

What are the reasons for the prominence of cognitive deficits in mental disorders? A plausible explanation is that there is probably a cognitive regulatory dysfunction occurring in the patients which is “separate” from the classical symptoms of these disorders (Etkin *et al.* 2013). Based on findings across neuropsychology and neuroimaging findings, Etkin *et al.* suggested that these deficits may either: 1. have been there to predispose individuals to develop the mental disorders, or 2. serve as an early marker of subsequent illness or 3. have a significant role in maintaining the disorder, and more importantly in terms of cognitive rehabilitation—may predict the likelihood of recovery (Etkin *et al.* 2013).

The prevailing nature of these cognitive deficits and the limited efficacy of psychotropic medications at ameliorating them in various neurocognitive and mental disorders (Erickson *et al.* 2005; Galletly *et al.* 2000; Keefe *et al.* 1999; Marder 2006; Sharma *et al.* 2006; Sharma & Antonova 2003) have led to the emergence of new treatment modalities in cognitive rehabilitation including the ones better known as “cognitive remediation therapy”.

2 COGNITIVE REMEDIATION THERAPY

An expert consensus group has defined cognitive remediation therapy (CRT) as “a behavioural-training based intervention that aims to improve cognitive processes (attention, memory, executive function, social cognition, or metacognition) with the goal of durability and generalization” (Benedict *et al.* 1994). In effect, however, CRT is not a homogenous approach or method. They may range from a simple “newspaper groups” to stimulate recall and thinking processes, to more sophisticated and high-end programs requiring hi-tech software and specialized training.

One way to understand what CRT is by classifying it into the main approaches used in treatment. Twamley *et al.* (Twamley *et al.* 2003) have divided CRT into four main approaches depending on the method used and the presence of a facilitator or “therapist”.

The first approach is “automated task practice” whereby CRT uses pencil-and-paper and other types of drills to target cognitive skills that were affected. It works on the basis that repeated practice on cognitive tasks may sharpen cognitive skills that have diminished due to mental illness.

The second approach is “strategy-oriented task practice” which uses task practice with strategy coaching. Here, the presence of a trained therapist and the presence of individualized treatment strategies is postulated to improve the outcome of the task practice.

The third approach is “computer-assisted automated task practice” whereby computer-assisted techniques are used extensively to improve cognitive abilities via repetition and practice drills.

The last one is “computer-assisted strategy-oriented task practice” where intervention is more personalized, and the presence of trained therapists is important to facilitate strategies required for individual patients. One popular model of this approach is the Neuropsychological Educational Approach to Cognitive Remediation (NEAR) introduced by Prof Alice Medalia (Medalia & Freilich 2008). It utilizes a combination of psychological principles such as neuropsychology, educational psychology, self-determination theory, and learning theories in combination with extensive use of educational apps and software to provide an ideal learning platform where patients can improve their cognitive function.

Ultimately, whatever approaches are used in CRT, the aim is not only to ameliorate cognitive deficits but to translate these improvements into restored psychosocial functioning.

There have been several postulations on how CRT works in remediating cognitive deficits. Two plausible explanations came from Heinssen *et al.* (Medalia & Freilich 2008) and Kurtz *et al.* (2007). Heinssen *et al.* proposed that CRT builds a higher “platform” for learning capacity enabling patients to respond better to the existing evidence-based psychiatric rehabilitation services (Kurtz *et al.* 2007). In other words, CRT serves to “prime” the patients’ cognitive faculty to enable them to respond better to complementing bio-psycho-social interventions offered to the patients. This makes a lot of sense because all CRT programs are not conducted in isolation but rather as an add-on to existing treatments which may include pharmacological treatment with antipsychotics, occupational therapy, social skills training, or vocational rehabilitation.

On the other hand, Kurtz *et al.* proposed that repeated practice on neurocognitive tasks strengthens neurocognitive skills or, enables patients to acquire compensatory strategies to circumvent areas of persistent difficulties leading to secondary improvements in “unpractised” neuropsychological tests that make similar demands (Kurtz *et al.* 2007).

3 EFFECTIVENESS OF COGNITIVE REMEDIATION THERAPY FOR MENTAL DISORDERS

The application of CRT for mental disorders especially for schizophrenia—the most severe form of mental disorders—emerged in the late 1990s through early 2000s. This was

especially boosted by the growing interest in finding effective interventions for residual cognitive deficits seen in people with schizophrenia (Gold & Harvey 1993; Wilk *et al.* 2005). By then cognitive deficits have already been concluded to be the “last” cluster of schizophrenia symptoms which have not been addressed sufficiently by the existing anti-psychotics (Marder & Fenton 2004).

How effective is CRT in ameliorating cognitive deficits? Over the last two decades, several meta-analyses have been done to review the effectiveness of CRT for schizophrenia (McGurk *et al.* 2007; Twamley *et al.* 2003; Wykes *et al.* 2012)—being that works on CRT in schizophrenia have been the most extensive among all mental disorders. Interestingly, the calculated effect sizes (Cohen’s *d*) of the efficacy of CRT for cognitive performance have shown improving trends, from 0.32 (small to moderate effect size) in 2003 (Twamley *et al.* 2003), to 0.41 (moderate effect size) in 2007 (McGurk *et al.* 2007), to 0.43 (moderate effect size) in the most recent available meta-analyses in 2011 (Wykes *et al.* 2012). More encouraging, however, is the fact that in all three meta-analyses, the effect sizes for improvement in psychosocial functioning were consistently around small to moderate—within scores which could be considered as “clinically significant”.

Studies on the effectiveness of CRT for other mental disorders are still considered preliminary but with similarly encouraging results. For instance, Listunova *et al.* (2020) found significant improvement in attention following CRT in a controlled study among partially remitted major depressive disorder patients. Another study using computerized CRT by Bajwa *et al.* (2019) among patients with the diagnosis of depression, anxiety, post-traumatic stress disorder (PTSD), and substance use disorder showed modest improvement in cognitive dysfunction but with a positive change in the self-esteem of the patients. Similarly, quite a number of studies have been done on eating disorders (Easter & Tchanturia 2011; Meneguzzo *et al.* 2021; Roberts 2018) with mixed outcomes but with a general trend of promising outcomes in terms of improving metacognitive ability and in transferring the skills to real life (Easter & Tchanturia 2011). Most of these programs follow the basic CRT approach originally developed for schizophrenia but modifications are necessary considering the heterogeneity of symptoms and presentations in the various disorders.

4 THE FUTURE OF COGNITIVE REMEDIATION THERAPY

Around the world, several studies are being done to explore the vast potential of CRT in improving cognitive deficits in various mental disorders including attention deficit hyperactivity disorder (ADHD) (Van der Oord *et al.* 2014), autism spectrum disorder (ASD) (Dandil *et al.* 2020), mild cognitive disorder and early dementia (Barekattain *et al.* 2016; Diaz Baquero *et al.* 2022) and cognitive stroke (Jung *et al.* 2021; Mingming *et al.* 2022; Xuefang *et al.* 2021).

At the same time, there are preliminary studies also being done to explore utilizing cutting-edge technologies such as enhanced reality approaches—virtual reality, augmented reality, or mixed realities in various forms of mental disorders (Aprile *et al.* 2020; Park *et al.* 2020). This makes complete sense considering that despite computer use becoming a common feature in many CRT programs, it still remains fairly “labour-intensive” considering the need for trained and dedicated personnel to guide patients to benefit fully from CRT. Shifting to the metaverse in the long run might be a more efficient way to improve efficacy and promote independence and self-learning which are both important to determine a better outcome of cognitive rehabilitation.

5 CONCLUSION

Cognitive remediation therapy is an evidence-based treatment aimed at ameliorating cognitive deficits in neuropsychological and mental disorders. The prospect of utilizing CRT as

an adjunctive treatment to the standard treatment of these disorders is great, considering that many mental disorders present with residual cognitive deficits. The future is very exciting with the potential of utilisation of cutting-edge technologies to enhance its efficacy.

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The effect of laughter therapy as a nursing intervention on reducing depression in elderly: Literature review

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ABSTRACT: Depression is one of the most common mental health issues among the elderly. Depression is characterized by persistent sadness, feelings of guilt, lack of confidence, and loss of interest. Stress in the face of changes in decreased ability or physical strength, as well as deterioration in health and physical illness, social position, finances, and income, causes depression in the elderly. Treatment and therapy efforts to improve the elderly's condition are required. Laughter therapy is a non-pharmacological therapy that can help the elderly reduce their levels of depression. Laughter makes people feel relieved, light, and happy. The goal is to determine the best method or steps for laughter therapy for the elderly in order to reduce depression. Methods: The study was conducted using the keywords "Laugh Therapy" AND "Depression" AND "Elderly," search articles in databases such as Google Scholar and Pubmed. From the 873 search results obtained, screening was performed, and six journals that matched the PICOT inclusion criteria, problems, and research objectives were obtained. According to six peer-reviewed journals, the majority of laugh therapy methods for the elderly employ laugh simulation and humor. Conclusion: Laughter therapy is an effective method for treating depression in the elderly. As a result, laughter therapy has the potential to be used as an intervention in nursing practice, particularly in nursing homes.

1 INTRODUCTION

Older adults are people who are over the age of 60. In older adults, physical, mental, and social changes occur. Physical changes such as a decrease in physical strength, stamina, and appearance as people age can make them unhappy and depressed. As a result, older adults are less productive in carrying out activities and social roles, impeding Indonesian older adults' healthy aging (Basrowi *et al.* 2021).

Older adults population according to Nations (2019) and WHO (2023) estimates that it will increase rapidly from 1.4 billion in 2030 to 2.1 billion older adults in 2050. In 2020, Indonesia faces an increase in the number of elderly people reaching more than 27 million people, or more than 10.6% of the Indonesian population are elderly, and could continue to increase to 13.8 % in 2035 (Indonesia 2022). Thus, the population aging around the world, including in developing countries such as Indonesia, could challenge healthcare providers, ensuring healthy aging.

Increasing age for everyone, including older adults, will provide an overview of the health status of the elderly themselves, both physically and mentally. The elderly must face various problems in their old age such as changes in social position, risk of disease, loss of work, and loss of loved ones (WHO 2022). These conditions make the elderly more vulnerable to experiencing mental problems such as depression (Thipprakmas 2021; Winahyu 2017).

Based on data released by the study of community-based mental health, the prevalence of the elderly population in the world who experience depression ranges from 10% to 20%

depending on culture (Thipprakmas 2021). Elderly people who experience depression are caused by feelings of loneliness that arise when they are away from their families because there are no longer people who have been living together and sharing everything. When feelings of loneliness arise, stressors increase and cause the elderly to reach the stage of depression (Alhalaseh *et al.* 2022).

In Indonesia, the prevalence of depression in the elderly varies and is high prevalence. Previous cross-sectional studies reported depression in older adults ranged from 33% to 48% (Anissa *et al.* 2019; Hartutik & Nurrohmah 2021). This is a very serious psychological problem, especially among the older adult population since untreated depression can lead to suicide (Conejero *et al.* 2018). According to the results of (Indonesia 2018), the age range of 15–24 years has begun to show depressive disorders with a prevalence of 6.2% which increases with age, the highest prevalence is at age >75 years by 8.9%, by age 65–74 years by 8.0% and by the age of 55–56 years by 6.5%.

Symptoms of depression can be indicated by depressed mood, loss of interest, feelings of guilt, low self-esteem, reduced self-confidence, eating disorders, sleep disturbances, lack of energy, and decreased concentration. Changes in roles decreased social interaction and job loss can make the elderly vulnerable to mental problems including depression (Fernández-Niño *et al.* 2018; Noguchi *et al.* 2021). Several factors cause the elderly to experience depression along with increasing life expectancy such as physical factors related to the presence of disease, psychological factors characterized by unresolved factors, and social factors in old age caused by the loss of loved ones and even loss of life work life (Fernández-Niño *et al.* 2018; Hung *et al.* 2021).

Handling depression in the elderly can be done in various ways, namely pharmacological or non-pharmacological. Pharmacological treatment is with antidepressant drugs that can help cytometrically, but cause adverse effects for the elderly if used for a long time (Taylor 2015), while non-pharmacological therapy, such as complementary therapy, could be used to promote the health of older adults (Dewi *et al.* 2022). For instance, some previous studies have been reported that complementary therapy benefits older adults' health and well-being (Fahriyah *et al.* 2021; Sharpe *et al.* 2007; Tay 2013). In particular, laughter therapy is reported as an effective intervention for reducing depression. The benefits of laughter therapy are to build relationships, relieve tension and anxiety, release anger, and overcome painful feelings (Yim 2016).

Laughter therapy causes the heart rate to become faster, blood pressure increases and oxygen levels in the blood will increase due to faster breathing, decreasing ACTH secretion (*Adreno Cortico Tropin Hormone*) and cortisol levels in the blood, decreased ACTH secretion will stimulate increased production of serotonin and endorphins released by the hypothalamus. Endorphins are neuropeptides that the body produces when relaxed. Endorphin hormones function as natural sedatives and provide a sense of comfort in the body. Endorphins are produced by the brain and spinal cord, serotonin causes a vasodilating effect on blood vessels which will eventually increase the circulation of O₂ throughout the body (Yim 2016; Yoshikawa *et al.* 2019).

Laughter therapy was chosen as one of the therapies to improve a person's ability to deal with mental conditions and in its implementation, there was a process of relaxation of the respiratory system. When humans experience stress or mental stress, the process of breathing is fast and, in a hurry, in this laugh, proper breathing techniques can circulate oxygen throughout the body's tissues, giving a calming effect on the mind. Laughter therapy also involves several people in laughter groups who spontaneously interact and provide support, thereby increasing interpersonal relationships and self-confidence (Nurwela *et al.* 2017).

Nurses have an important role as educators for elderly people who are depressed. Nurses help clients by providing health knowledge, symptoms of illness, and prevention that can provide behavioral changes in clients. In addition, the role of nurses as motivators can raise enthusiasm and reduce feelings of hopelessness and helplessness so that the elderly can feel a sense of security and love in the orphanage environment. The nurse's role as a counselor is help clients to realize and overcome psychological pressure or social problems, build good interpersonal relationships, and improve their mental health (Nance 2012).

Although much evidence has been found regarding the effectiveness of laughter therapy in reducing depression rates in the elderly, a recent systematic review for firmer conclusions regarding the procedures or Standard Operational Procedures (SOP) that can be used has not been widely carried out. Therefore, it is necessary to summarize the literature that aims to identify the procedure or SOP for laughter therapy as a nursing intervention to reduce depression levels in the elderly.

2 METHODS

This literature review search used two databases. The databases used in the literature search are Google Scholar and Pubmed. This study used the PICOS/T Framework. This method can be used to find an article with the following criteria: (a) Population/Problem, in this Literature Review is the elderly who are depressed; (b) Intervention, action in the Literature Review, namely laughter therapy; (c) Comparison, there is no comparison in the Research; (d) Outcome, laughter therapy as a nursing intervention to reduce depression in the elderly; (e) Study Design, Quasi experiment and pre-experiment; (f) Time in the reviewed article is stated in the last 5 years (2016–2021).

To making it easier to determine the journal to be used, the search for articles or journals can use keywords or Boolean operators to specify and expand the search. “laughter therapy AND depression AND elderly” are the keywords used in this literature review.

3 RESULTS

According to the results of a literature search using keywords that have been adapted to the MeSH and PICO databases in the last 5 years, the researchers found 694 journals or articles in Indonesian and English that match these keywords. Furthermore, the search was narrowed, and the researchers then screened based on the title and relevance to the literature review theme, obtained from 27 journals. Identification is done based on standard inclusion and exclusion criteria; the results obtained are as many as journals that can be used in the literature review which can be seen in Figure 1.

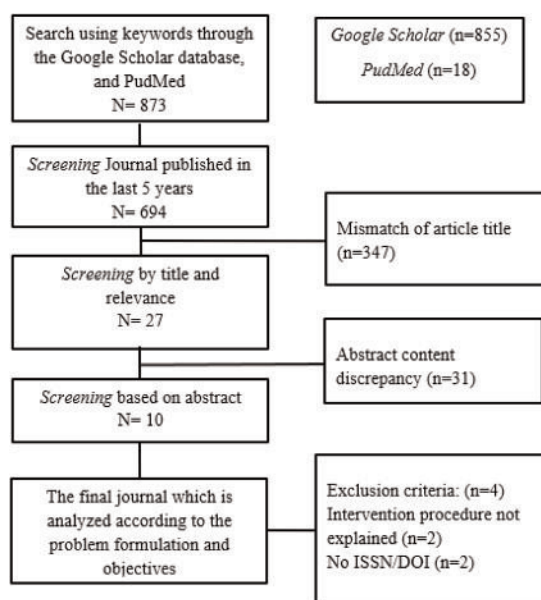


Figure 1. Literature review search results.

4 DISCUSSION

According to six previous studies that have been reviewed by researchers, it found several facts regarding the age of the respondents, indicating that most of the older adults who experienced depression were over >60 years old. This is in accordance with the results of Anita & Linda (2018) that the average age of the elderly experiences depression in the age >60 years. Moreover, this is also in accordance with the previous study that reported older adults are prone to depression, and who live in nursing homes had higher depression rates than those living with their families (Šare *et al.* 2021).

Age is one of the factors related to depression. With increasing age, the risk of depression will also be doubled because at that time a lot of changes occur in a person. These changes are physical, psychological, economic, social, and spiritual changes that affect the quality of life of older adults (Silalahi *et al.* 2022). According to the opinion of researchers, as a person age, they will experience changes physically, psychologically, economically, socially, and spiritually which affect the quality of life of the elderly so that they can be at risk of depression.

The second fact is found in the journals reviewed Umamah & Hidayah (2017), namely the research sites on average in social/nursing homes where many elderly people who experience depression live in nursing homes. This study, which observed and communicated with eight elderly people, showed that 62.5% appeared with sad facial expressions, looked aloof, and were depressed due to never being visited or thought of their wife, children, and family.

In general, older adults living in nursing homes are found to be prone to depression. Due to the lack of ability to adapt psychologically to changes in environmental stress can cause depression. They think that their lives have failed because they have to spend their lives far from loved ones, causing the elderly to have difficulty adapting to conditions in the orphanage and negative adjustments. According to social relations with family and surroundings, reduced social interaction with loved ones can cause feelings of worthlessness, feeling excluded, and no longer needed (Nurwela *et al.* 2017).

The third fact is where the instrument used to measure the level of depression in the elderly, namely in four studies using the Geriatric Depression Scale (GDS), while two studies using DASS 42 (Depression, Anxiety, Stress Scale) and the Beck Depression Inventory (BDI). Based on the study of Siregar & Gultom (2019), the Geriatric Depression Scale-15 for the Indonesian version short form GDS-15. The instrument has 15 items with scores ranging from 0 to 15 that are classified into three levels of depression groups: minor (<5) mild (5–9), and severe (10–15) (Sheikh & Yesavage 2014), the short form GDS-15 has a sensitivity accuracy rate of 84% and a specificity value of 95% (de Craen *et al.* 2003). The instrument could be used to adequately assess depression in older adults and GDS is also widely used to assess the mental health of older adults in Indonesia.

The fourth fact is related to laughter therapy procedures in six reviewed articles, the majority of laugh therapy procedures use laugh and humor simulation methods. The elderly were given laughter therapy with a duration of 10–15 minutes, carried out with a warm-up exercise technique, showing a video with a duration of approximately 5 minutes and the elderly could laugh out loud for approximately 15 seconds. Hence, this laughter therapy was carried out four times in 15 seconds for one week.

The majority of the stages of implementing laughter therapy were adopted from (Kataria 2011) as follows: 1) Warm up first by inhaling through your nose, and holding your breath for 15 seconds with belly breathing. Then exhale slowly through the mouth. Do it three times in a row. 2) Then the therapy guide suggests to the group that therapy will be started. 3) The guide then laughs loudly (haa-haa-haa-hii-hii-huu-huu) and is followed by group members facing each other, face to face, and laughing at each other. 4) This laugh can last as long as 15 seconds. After 5 minutes, laugh again (voicing hii-hii-hii). If it is not compact, do it again by voicing (huu-huu-huu). Until all compact while doing laughter therapy exercises. 5) After

Table 1. Previous Studies Effect of Laughter Therapy on Older Adults' Depression

No	Author	Title	Results
1.	(Umamah & Hidayah 2017)	The Effect of Laughter Therapy on Depression Levels in the Elderly at the Uptd Griya Wreda Orphanage, Surabaya	The results showed that before being given laughter therapy, almost half of 35.7% experienced moderate depression and after being given therapy, almost half of the respondents 35.7% were normal/not depressed. The results of the Wilcoxon test on laughter therapy obtained a value of = 0.000 and the value of = 0.05 means < then H0 is rejected, which means that there is an effect of laughter therapy on depression levels in the elderly in nursing home.
2.	(Pradnyadiansari <i>et al.</i> 2017)	Laughter Therapy Reduces Depression in the Elderly.	The results of the study before giving laughter therapy more than 50% (55%) of respondents experienced moderate-severe depression. After the laughter therapy was given, most of the 68% of respondents experienced mild depression. 12.5% of respondents did not experience a change in the level of depression. The results of the Wilcoxon test with a significant level of = 0.05 and a price of p = 0.000, p-value <then there is an effect of laughter therapy on the level of depression in the elderly.
3.	(Anita & Linda 2018)	The Effect of Laughter Gymnastics Therapy on Depression Levels in the Elderly at the Tresna Werdha Budi Sejahtera Social Home, South Kalimantan Province, Banjarbaru	The results of the study before being given laughter therapy, 15 respondents who experienced mild depression, after being given laughter therapy, none of the respondents experienced mild depression. The results of the Wilcoxon Signed Rank Test showed p = 0, 000 with a = 0.05 there was an effect before and after being given laughter therapy.
4.	(Siregar & Gultom 2019)	Effect Of Laughter Therapy on Depression Level in Elderly in a Nursing Home, North Sumatra, Indonesia	The results showed that the level of depression in the elderly decreased significantly in the experimental group (P<.05). There is an effect of laughter therapy on reducing depression levels in the elderly.
5.	(Amin <i>et al.</i> 2019)	The Effect of Laughter Therapy on Decreasing Depression Scores in the Elderly at UPTD Rumoh Sejahtera Geunaseh Sayang Ulee Kareng, Banda Aceh City.	The results of the statistical test show a P value of 0.001, which means if there is a difference between depression before and after being given laughter therapy at UPTD Rumohh Sejahtera Geunaseh Sayang Ulee Karaeng City Banda Acehh City in 2019.

(continued)

Table 1. Continued

No	Author	Title	Results
6.	(Ulahannan & Xavier 2017)	The Effect of Laughter Therapy on Depression In Elderly Residents Of Selected Old Age Home From Maharashtra.	There was a significant change between pretest depression scores and posttest depression scores in the experimental group using the t-test. the mean score for the pretest was 44.8, which was significantly reduced in the post-test to 9.9. while in the control group, there was no change. So that it can be shown that laughter therapy is effective in reducing depression experienced by elderly residents of Maharashtra nursing homes.

heating, the guide provides media for laughter therapy using funny videos. 6) Then do it 4 times a week for 15 seconds at 09.00 am.

Based on the theory, laughter therapy is laughter that begins with step by step, so the effects of laughter therapy are felt to be really useful and have been done by many people. Laughing for 5–10 minutes can encourage the release of endorphins and serotonin, a type of body's natural morphine. Both substances are good for our brain so we feel calmer. Besides being easy to do, laughter therapy has a great effect, it can even heal patients with mental disorders due to severe stress (Šare *et al.* 2021). Laughter can be produced from humor or laughter therapy carried out in groups and this laugh can last 15 seconds.

This is in accordance with findings from several previous studies showed that laughter therapy is a mental or emotional expression that is shown through facial expressions and certain sounds (Šare *et al.* 2021; Siregar & Gultom 2019; Umamah & Hidayah 2017). Laughter is a reaction to a certain stimulus that can be seen in the expression of happiness or feelings of pleasure. When you laugh, your body will release endorphins that make your body feel comfortable (as a natural sedative), reduce stress hormones, and increase feelings of happiness. Endorphine is a hormone released by the hypothalamic pituitary adrenal (HPA) gland, one of the hormone-producing glands under the hypothalamus and this hormone will be secreted when a person feels comfortable and relaxed (Yim 2016).

Then the increase in endorphins produced in laughter therapy will have a positive impact on a person's psychological and physical such as suppressing emotions or mental stress, improving interpersonal relationships, increasing self-confidence, increasing social relationships, stimulating the heart and blood circulation, increasing immunity so that laughter will affect the pituitary gland in the brain to release endorphins (Yim 2016). Endorphins can provide a sense of relaxation and calm so as to reduce depression.

Notably, the techniques in laughter therapy can be applied to the elderly and are easy to do. This therapy can be done with family, elderly with caregivers, or in groups. Laughter therapy that is carried out gradually and regularly can have a positive impact on the mental health of the elderly. Therefore, researchers suggest laughter therapy as a non-pharmacological intervention to reduce depression levels in the elderly, with laughter therapy making the elderly able to express and express feelings and be happy.

5 CONCLUSIONS AND SUGGESTIONS

According to six reviewed articles, it can be concluded that currently the majority of laugh therapy procedures in the last 5 years use the laugh simulation method and humorous video humor adopted. The stages of implementing laughter therapy are as follows: 1) Warm up first by inhaling through your nose, and holding your breath for 15 seconds with belly breathing. Then exhale slowly through the mouth. Do it three times in a row. 2) Then the therapy guide suggests to the group that therapy will be started. 3) The guide then laughs loudly (haa-haa-haa-hii-hii-huu-huu) and is followed by group members facing each other, face to face, and laughing at each other. 4) This laugh can last as long as 15 seconds. After 5 minutes, laughing again (voicing hii-hii-hii). If not compact, do it again by voicing (huu-huu-huu). Until all compact while doing laughter therapy exercises. 5) After warming up, the guide provides media for laughter therapy using funny videos. 6) Then do it 4 times a week for 15 minutes at 09.00 am.

A complementary therapy would be included in nursing interventions for older adults suffering from depression. Complementary therapy is a type of non-biomedical therapy that includes a variety of actions that can be performed independently. Laughter therapy is one of the complementary therapies that can be used to treat depression in older adults. The benefits of this laughter therapy are that there is no specific preparation, it does not take a long time, and it does not require a fee, but rather eye contact and active participants in laughter therapy, which makes it good for the elderly and effective in reducing depression levels in the elderly.

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Analysis of nutritional status in stunted children (0–5 years)

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ABSTRACT: Stunting is a global development problem that jeopardizes physical and cognitive development and economic productivity. Stunting cases in Indonesia are pretty high; although it decreased in 2019 to 27.67%, stunting reduction efforts are still being carried out intensively. Monitoring of nutritional status needs to be done regularly to determine the success of interventions. This study aimed to describe the nutritional status of stunted children aged 0–5 years in Tegal City. This study was a descriptive survey with a retrospective approach. Cluster sampling was used 187 stunting children. We collected the data from November to December 2021 and analyzed it using univariate tests. The results showed that most stunting was found in boys (55.6%). Most stunting cases were children with shorter stature (64.7%). The nutritional status of stunting children is mostly normal so that interventions are only carried out in stunting cases. However, there were minor cases where 3.2% of stunting children were obese. There is a need for government policies to declare cross-sectoral programs to reduce stunting rates. Health workers need to be more aware of stunting cases with obesity.

1 INTRODUCTION

The high prevalence of stunting in children is a global problem related to poverty (Vaivada *et al.* 2020). Stunting in children has a considerable impact on countries where children will experience delays in physical and mental development and can also pass on stunting cases to their generation (Tasic *et al.* 2020). Stunting also causes an increased risk of obesity (Kang *et al.* 2018), cognitive delay (Blankesndhip *et al.* 2020), affects learning performance, and has a long-term impact on economic productivity (Li *et al.* 2020). In addition, stunting is one of the causes of the death of as many as one million children every year. Therefore, reducing the incidence of stunting is an important and urgent matter to be handled (Asmamaw *et al.* 2020).

Based on World Bank data, globally, the prevalence of stunting in 2020 was 20.011% (WHO, UNICEF, UNFPA 2020). This coverage has reached the Joint Child Malnutrition Estimate (JCME) target, which is 22% in 2021. Meanwhile, Southeast Asia has the highest prevalence compared to other sub-regions in Asia. Southeast Asia has a stunting prevalence of 27.4% in 2020. This coverage is higher than the prevalence in Asia, 24.5% (Fentiana *et al.* 2021). Indonesia is one of the countries in Southeast Asia with a reasonably high stunting problem (Anam & Saputra 2021). The prevalence of stunting in Indonesia has decreased; wherein 2018, the prevalence of stunting reached 30.8% and decreased to 27.67% in 2019 (Statistik 2019). To deal with the problem of stunting, the government has issued policies involving many sectors such as strengthening food, developing an information data center, improving health for pregnant women, nutrition interventions, intervention in the first 1000 days of birth (Hartotok *et al.* 2021).

Handling stunting is also carried out by increasing parents' understanding of the importance of fulfilling nutrition during pregnancy and exclusive breastfeeding. Monitoring the growth and development of stunted children also needs to be done regularly by paying attention to weight for age, height for age, and weight for body length (Permana *et al.* 2021). Monitoring is vital to do so that stunting is adequately implemented. Inadequate handling can lead to unattainable improvement of the condition in children (Bukari *et al.* 2020). Monitoring nutritional status is vital in handling stunting cases.

Thurstans *et al.* in their review stated that the majority of stunted children have a high risk of experiencing malnutrition (Permatasari & Chadirin 2022; Thurstans *et al.* 2022). However, the majority of studies only focus on the determinants of stunting (Asmamaw *et al.* 2020; Beal *et al.* 2018; Blankesndhip *et al.* 2020; Corsi *et al.* 2016; Mengesha & Haile 2022; Shibre *et al.* 2021; Siswati *et al.* 2022; Sufiyan *et al.* 2012; Thurstans *et al.* 2022), stunting prevention, and treatment efforts (Bhutta *et al.* 2020; Dewi & Aminah 2016; Huriah *et al.* 2020; Kohli *et al.* 2020; Latifah *et al.* 2020; Permana *et al.* 2021; Sufiyan *et al.* 2012; Tasic *et al.* 2020). Currently, stunting with obesity is starting to be detected (Henriques *et al.* 2018; Lee & Yoon 2018). Studies related to monitoring stunted children's nutritional status have never been done comprehensively, only focusing on malnutrition status (Bukari *et al.* 2020). The problem of obesity in stunting children is rarely found, but it needs to be prevented from the start. Therefore, this research was conducted to identify the nutritional status of stunted children in Tegal City in 2021. By identifying the nutritional status of stunted children, it is possible to know the appropriate management based on their nutritional status and can indirectly prevent an increase in stunting cases with obesity.

2 METHODS

This study was quantitative. We used a descriptive survey with a retrospective approach to describe nutritional cases of stunted children in Tegal City through data from the integrated stunting prevention information system or SSGBI. The collection of stunting status data was scheduled every February and August every year. Therefore, the data used in this study was secondary data obtained from stunting data reported in August 2021. The population was all children aged 0–5 years diagnosed with stunting at the Integrated Healthcare Center or the first health facility and reported to the SSGBI (Statistik 2019). The sampling technique used was cluster sampling. This study selected the sample by classifying stunting children based on the Public Health Center that handled stunting with the highest, lowest, and moderate number of stunting cases (Taherdoost 2016). The Public Health Center with the highest stunting cases was the Tegal Timur Public Health Center, and the lowest cases were in the Slerok Public Health Center. While the moderate stunting cases were in the South Tegal Public Health Center, the number of respondents in this study was obtained as many as 187 respondents. Data collection was carried out from November to December 2021. The instruments used in this study were field notes and dummy tables—analyzed data using univariate analysis to identify stunting status.

3 RESULTS AND DISCUSSION

This study was conducted to identify the nutritional status of stunted children. Parameters of nutritional status of children under five were calculated using the formula weight for age and weight for height (Kohli *et al.* 2020). While stunting was assessed from height for age (Shibre *et al.* 2021). This research was conducted in three public health centers with various cases, and the characteristics of the respondents were as follows:

Table 1. The characteristics of respondents.

Variable	f	%
Public Health Center		
Tegal Timur	126	67.4
Tegal Selatan	47	25.1
Slerok	14	7.5
Age when measured (years old)		
0	6	3.2
1	25	13.4
2	55	29.4
3	47	25.1
4	43	23.0
5	11	5.9
Sex		
Boy	104	55.6
Girl	83	44.4
Height for Age		
Severe stunted	121	64.7
Stunted	66	35.3
Weight for Age		
Severe undernourished	52	27.8
Undernourished	82	43.9
Normal	53	28.3
Weight for Height		
Severe wasted	3	1.6
Wasted	56	30.0
Normal	122	65.2
Overweight	6	3.2

Most cases of stunting were found in boys (55.6%). Several studies showed that most stunted children in South Asian and Southeast Asian countries were boys, including in Indonesia (Gani *et al.* 2020; Thurstans *et al.* 2020). Boys are biologically more vulnerable than girls. Boys are easily influenced by stressful environments (Mengiste *et al.* 2020). However, due to the limited number of respondents, this result cannot be ascertained whether sex is a factor causing stunting; to determine whether males are a predisposing factor for stunting, it needs further study by comparing stunting cases throughout Tegal City or comparing with the same region and characteristics (Thurstans *et al.* 2020).

The majority of respondents have had stunting screening for 0 months. This was done to detect the risk of stunting earlier so that immediate treatment could be carried out (Nurlita *et al.* 2021). The results of previous studies also found an increase in stunting cases in children < 2 years. Stunting under two years showed a significant association with children's cognition at the age of 5–11 years (Vaivada *et al.* 2020). The finding of stunting in children < 2 years old can be influenced by nutritional fulfillment during pregnancy, risky pregnancies, birth weight, gestational age, and history of non-exclusive breastfeeding (Alam *et al.* 2020). Age under two years is the most appropriate opportunity to provide intervention in stunting to minimize delays in children's cognitive development (Pal & Bose 2020).

Based on the results, it was found that respondents aged 3–4 years (48.1%) still experienced stunting. Stunting detected at this age is classified as late-onset. However, the potential for cognitive development delays is smaller than stunting detected under two years. In addition, the handling of stunting at this age is more accessible; most children are stunting-free at the age of 4.5–6 years (Alam *et al.* 2020).

The nutritional status of children is calculated from weight for age. Table 1 shows that most respondents (43.9%) were undernourished. This parameter is often used to monitor the children's nutritional status (Thurstans *et al.* 2020). Nutritional status is often associated as a factor causing stunting. The presence of nutritional deficiencies in the body affects a child's growth. Nutritional deficiencies also increase the risk of infection. Children who have infections tend to lose their appetite, so nutrients are mainly used for recovery rather than growth (Maulida & Prastiwi 2020).

Most stunted children were well-nourished; it shows that children only have stunting problems. Furthermore, undernourished children are still receiving treatment to improve child nutrition. However, in Table 2, there are cases of stunting children with overweight or obesity. A previous study stated that stunting cases with obesity are generally found in children who have received previous nutritional treatment, but experience metabolic changes, which cause an increased risk of obesity. Stunting can cause interference with the fat oxidation process so that the incoming nutrients cannot be broken down into energy (Atsu *et al.* 2017). It shows that chronically malnourished children can develop into decompensation or overweight, depending on environmental conditions and the characteristics of the child (Ferreira 2020).

Table 2. Frequency distribution of nutritional status of stunted children.

	Height for Age		Total
	Shorter	Short	
Weight for Age			
Severe Undernourished	22 (42.3%)	30 (57.7%)	52 (100%)
Undernourished	52 (63.4%)	30 (36.6%)	82 (100%)
Normal	47 (72.3%)	6 (27.7%)	53 (100%)
Weight for Height			
Severe Wasted	1 (33.3%)	2 (66.7%)	3 (100%)
Wasted	26 (46.4%)	30 (53.6%)	56 (100%)
Normal	91 (74.6%)	31 (25.4%)	122 (100%)
Overweight	3 (50%)	3 (50%)	6 (100%)

Stunting with obesity is short but has a fat body (Ferreira 2020). Henriques *et al.*, in their study, stated that stunting children with obesity had nutrition improvement, and the incidence of infection or illness decreased. The child's weight increased, but not their height. Stunting conditions also have a relationship with obesity in adulthood (Henriques *et al.* 2018). Considering obesity is one of the effects of stunting treatment, it is necessary to re-evaluate the treatment given to chronic stunting children. Because if stunting cases with obesity increase, the child morbidity will be higher. Children will be at risk for obesity in adulthood, increasing the risk of type 2 diabetes, cardiovascular disease, chronic kidney disease, and cancer. Obesity also increases mortality and premature mortality (Lee & Yoon 2018).

In handling stunting, health workers need to consider maternal history, especially in children with stunting under the age of 2 years. Therefore, handling should not only focus on improving nutritional status but also focus on increasing children's physical activity to minimize the occurrence of stunting with obesity (Lee & Yoon 2018). Government support through policies is also needed, especially supporting programs outside of health programs such as providing children's physical activity facilities, providing road facilities, improving sanitation, and so on (Palutturi *et al.* 2020).

4 CONCLUSION

Stunting detection in Tegal City has been carried out since children were 0 months old to handle stunting early. Most stunting cases are found in boys, but to justify sex as a predisposition factor for stunting, it needs further study by comparing stunting cases in areas with the same characteristics. Most stunted children were well-nourished. However, there are cases of stunting with obesity. This dual problem of malnutrition, even though it is a minor case, needs to be prevented and treated so that the prevalence does not increase. The policy implications of supporting stunting management need to be reviewed by paying attention to stunting cases with obesity. The implications of the research need further research to identify the factors of stunting with obesity and the interventions that have been accepted to obtain best practices in handling stunting with obesity.

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The effect of peer counseling on knowledge and motivation of pregnant women in stunting prevention

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ABSTRACT: Stunting is a chronic malnutrition problem characterized by short body posture and influenced by nutritional intake from the womb period. The low knowledge and motivation of pregnant women regarding stunting can be improved through Peer Counseling. This study aims to determine the effect of Peer Counseling on the knowledge and motivation of pregnant women in preventing stunting. This study used a Quasi Experiment one-group pretest-posttest design. Purposive sampling with 50 respondents. The level of knowledge and motivation was measured using a questionnaire at the pretest-posttest. Peer Counseling has been done with the lecture method through mentoring using leaflets. The test of differences in respondents' knowledge level before Peer Counseling was carried out was moderate (37.4%). After being assisted, the category increased (80.8%). The test for the difference in the level of motivation of respondents in stunting prevention before (pre-test) peer counseling was carried out in the medium (50.4%) and after (post-test) high category (92.8%). The analysis using a t-test showed an increase in knowledge and motivation regarding stunting prevention before and after peer counseling ($p = 0.000$). It is concluded that Peer Counseling can increase the knowledge and motivation of pregnant women to prevent stunting.

1 INTRODUCTION

Stunting is the impaired growth and development that children experience from poor nutrition, repeated infection, and inadequate psychosocial stimulation. Children are defined as stunted if their height-for-age is more than two standard deviations below the WHO Child Growth Standards median (World Health Organization 2020). Stunting sufferers are generally susceptible to disease and have a below-normal level of intelligence and low productivity. Indonesia's stunting rate is fourth in the world and second in the Southeast Asia region. According to WHO standards, the maximum tolerance limit for stunting is 20 percent or one-fifth of the total number of children under five who are growing, while Indonesia is still at 27.67 percent (Cobham 2013).

One of the causes of stunting is low nutritional intake in the Golden Period of 1000 First Days of life, from the fetus to the baby aged two years (Ministry of Health of the Republic of Indonesia 2018). Prevention of stunting can be started during pregnancy, especially since the Golden Period of 1000 First Days for life, by increasing the mother's knowledge about the health and nutrition of pregnant women through counseling during antenatal care visits (Nurfatimah *et al.* 2021).

According to research by Alfarisi *et al.* (2019), mothers with chronic energy shortage during pregnancy had a 2.2 times higher risk of stunting in children under five than mothers with adequate nutritional conditions. A poor nutritional status before birth will affect a person's later life, including stunted fetal growth, low birth weight, and short, thin kids, as well as standard immune systems and a higher risk of death. There were 228 low-birth-weight infants (under 2500 grams) in Surakarta City in 2019, according to records from primary healthcare. Low birth weight cases were most prevalent in the local healthcare system found in the Sangkrah Health Center area, with 36 babies (4%).

Community involvement in stunting prevention efforts has a long-term impact. These efforts can be accomplished through education, information, joint decision-making, through participatory counseling activities. Peer counseling aims to empower individuals to effectively support one another in coping with health concerns. Information delivery and knowledge transfer can be done more quickly using simple language (Varenhorst 2016).

This counseling is held as an activity forum for pregnant women to exchange knowledge, with one person as a resource who provides information to other participants. The effectiveness of this peer counseling activity in educating pregnant women has been demonstrated. Participants will be helped to understand the main topic through the media utilized in peer counseling. Participants in the peer counseling activity can share knowledge-enhancing information, inspiring them to complete the pregnancy nutrition requirements to prevent stunting.

Based on the problems related to stunting, increasing knowledge of pregnant women is one strategy to prevent stunting, primarily through peer counseling for pregnant women.

2 METHODS

This research is a quasi-experimental study based on One-Group Pretest-Posttest Design. The sampling technique was carried out using the purposive sampling method with the inclusion criteria of respondent. The population sampled in this study was under the criteria of as many as 50 people. The study population was all pregnant women who took pregnancy classes in the Sangkrah Health Center and Gambirsari Health Center in 2022.

Data were collected using questionnaires divided into two types, knowledge and motivation regarding stunting. The research will be carried out in May-September 2022 at Sangkrah Health Center and Gambirsari Health Center. Respondents were asked to complete a questionnaire to measure their knowledge and motivation regarding stunting. The questionnaire distributed for the pretest and posttest is the same, consisting of 2 parts. There is an 18-point questionnaire about respondents' knowledge and 16-point questionnaire related to respondents' motivation towards stunting prevention. The questionnaire that had been tested for validity and reliability. Peer counseling was carried out every week and total 4 times. The researcher conducted peer counseling using lecture and leaflet methods in the antenatal pregnancy class in primary health care. One month after peer counseling was conducted, respondents were re-measured in their level of knowledge and motivation using the same questionnaires. Analysis was conducted in paired sample t-test using SPSS 22.

3 RESULTS

Based on the Table 1, data on the characteristics of respondents were obtained, the majority of pregnant women who participated in this study were aged 20–25 years (34%), had junior high school education was 19 people (38%), Housewife background was 29 people (58%), first pregnancy was 20 people (40%), have not had children as many as 20 people (40%) and have never had a miscarriage as many as 48 people (96%).

Table 1. Characteristics of research respondents.

No	Information	Characteristics	N	Percentage (%)
1.	Age	<20 years	3	6.0
		21–25 years old	17	34.0
		26–30 years	13	26.0
		31–35 years	11	22.0
		>35 years old	6	12.0
2.	Education	Primary High School	2	4.0
		Junior High School	19	38.0
		Senior High School	17	34.0
		3 Diploma	5	10.0
		Bachelor degree	7	14.00
3.	Work	Housewife	29	58.0
		Private	7	14.0
		entrepreneur	8	16.0
		farmer	6	12.0
4.	pregnant to-	1	20	40.0
		2	15	30.0
		3	11	22.0
		4	4	8.0
5	live child	0	20	40.0
		1	17	34.0
		2	10	20.0
		3	3	6.0
6	Miscarriage	Never	48	96.0
		1	2	4.0

Table 2. Results of the t test knowledge and motivation of pregnant women towards stunting prevention.

		Paired Differences			Sig. (2-tailed)
		Mean	95% Confidence Interval of the Difference		
			Lower	Upper	
Pair 1	Pretest knowledge – posttest	–42.62500	–45.48886	–39.76114	.000
Pair 2	Pretest posttest motivation	42.434	62.5918	–20.12381	.000

Based on the output pair 1 obtained the value of sig. (2-tailed) of $0.000 < 0.005$, it can be concluded that there is a difference in the average pre-test and post-test of pregnant women's knowledge about stunting. Based on the output pair 2 obtained the value of sig. (2-tailed) of $0.000 < 0.005$, it can be concluded that there is a difference in the average pre-test and post-test motivation of pregnant women regarding stunting.

4 DISCUSSION

The respondents aged between the productive age range of 20–25 years old, so they are not included in the risky pregnancy category (<20 years or >35 years). The ideal age for women to get pregnant is between the ages of 20 and early 30. When entering the age of 35 years, a woman's fertility rate generally decreases, thus affecting the number and quality of eggs

produced (Sukma *et al.* 2020). Fulfilling nutrition during pregnancy is one of the initial efforts to prevent stunting before giving birth. Pregnant women must meet the needs of macro-nutrients in the form of carbohydrates, fats, proteins, vitamins and minerals. (Bloem *et al.* 2013). Optimal nutrition intake during the breastfeeding phase certainly fulfills good nutrition for infants to prevent stunting (Croockston *et al.* 2011).

Respondents in this study were mothers in their first pregnancy or never had a miscarriage. Dewi's research in 2021 shows that during her first pregnancy, the mother will be more attentive to her pregnancy. Mothers will be more interested in finding new information related to their pregnancy. On the other hand, mothers do not have sufficient experience and ability to take care of children during the first pregnancy. Providing adequate guidance and information about pregnancy and caring for babies is necessary, especially in terms of fulfilling nutritional needs for stunting prevention (Dewi *et al.* 2021).

Stunting in early life particularly in the first 1000 days from conception until age two impaired growth has adverse functional consequences on the child. Those consequences include poor cognition and educational performance, low adult wages, lost productivity when accompanied by excessive weight gain later in childhood, and an increased risk of nutrition-related chronic diseases in adult life (Mahmudah 2020). Linear growth in early childhood is a strong marker of healthy growth associated with morbidity and mortality risk, non-communicable diseases in later life, and learning capacity and productivity. It is also closely linked to child development in several domains, including cognitive, language, and sensory-motor capacities (Fikadu 2014).

Based on the T-test obtained, the value of Sig. (2-tailed) of $0.000 < 0.005$, it can be concluded that there is a difference in pregnant women's average pre-test and post-test knowledge regarding stunting. Peer counseling is an effective method to increase the knowledge of pregnant women about stunting. As explained, there is a relationship between the level of a mother's learning on knowledge, action, and mindset in finding and obtaining various data about toddler nutrition. Besides that, work also becomes one of the factors affecting knowledge. The type of work generally reflects the level of economic status. Families with middle to low economic status allow consuming foods with low nutrition, affecting children's nutritional status (Supariasa *et al.* 2012).

The results of a study by the Indonesian ministry stated that one factor that triggers stunting is insufficient knowledge and inappropriate nutrition practices. Diet is important because it is closely related to nutritional conditions, especially the quality and quantity of food eaten. The diversity of types of food eaten will affect the quality and completeness of various nutrients to the quality and completeness of nutrients that will meet the needs. The results of research by Samuel *et al.* (2017) found that children who are not stunted have a more diverse menu than children who are stunted. Not only that, there is a comparison between the consumption of macronutrients, energy, and protein and the consumption of micronutrients such as vitamin C, calcium, and phosphorus between stunted and non-stunted children (Samuel *et al.* 2017). One of the ways to increase mothers' knowledge is peer counseling mothers to alleviate stunting problems in Indonesia. Peer counseling is one of the counseling methods by peer tutors and is a part of health learning activities.

Based on the T-test obtained, the value of Sig. (2-tailed) of $0.000 < 0.005$, it can be concluded that there is a difference in pregnant women's average pre-test and post-test motivation regarding stunting. Peer counseling can increase the mother's motivation to prevent stunting. In this case, the mother's motivation also affects the pattern of behavior in preventing stunting. McDonald defines motivation as a change in a person's energy characterized by the emergence of feelings and preceded by a response to the existence of a goal. He suggests that individual needs to learn from the cultural environment. Hence, motivation, which is sourced from efforts to meet needs, is something that can be learned and taught. The growth of the mother's motivation for stunting prevention will encourage positive attitudes in efforts to fulfill nutrition during pregnancy and after the baby is born to prevent stunting (Andriani 2017).

5 CONCLUSION

Peer counseling increased the knowledge and motivation of pregnant women regarding stunting prevention ($p < 0.000$). The peer counseling method is carried out through lectures and leaflets given to pregnant women, effectively increasing the knowledge and motivation of pregnant women toward stunting prevention.

Health workers, especially midwives, are expected to increase the knowledge and motivation of pregnant women regarding stunting prevention, one of which is through peer counseling. Pregnant women are expected to prevent stunting by paying attention to nutrition from the time the fetus is in the womb, doing early initiation of breastfeeding, providing exclusive breastfeeding, routinely monitoring the growth and development of children, and meeting the nutritional needs of children.

The limitation of this study is that peer counseling was only carried out once. For further research, it is expected to carry out routine peer counseling within a certain period using a more diverse media to increase respondents' knowledge and motivation regarding stunting.

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Factors that influence adolescent attitudes towards sexual behavior to prevent pregnancy

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ABSTRACT: Adolescence is a period of rapid physical, psychological, and cognitive development. Adolescents are marked by a high level of curiosity and a desire to take risks for their actions without careful consideration. If they make the wrong decisions in the face of conflict, they will engage in risky behavior, and the long and short-term consequences of various physical and psychosocial health problems will be detrimental. Adolescent reproductive health is impacted negatively by adolescent problems such as pregnancy, marriage, young age, and high abortion rates. The purpose of this research is to determine the factors that influence adolescent attitudes toward sexual behavior in order to prevent pregnancy. An observational research design with a cross-sectional approach is used in this type of quantitative analytical research. The participants in this study were SMK Bhakti Husada Brebes students with a sample of 40 people with a purposive sampling technique, namely the selection of samples based on subjective and practical considerations. Collecting data through structured interviews using interview guidelines. The chi-square analysis test results revealed factors related to adolescent attitudes toward sexual behavior to prevent pregnancy, that is knowledge, parental roles, and sexual behavior, while the sources of information and history of sexual relations showed no relationship. Parents are expected to increase awareness about adolescent attitudes towards sexual behavior so that they can prevent pregnancy from an early age.

1 INTRODUCTION

Adolescence is a time of rapid physical, psychological, and intellectual growth and development. Adolescents are known for their insatiable curiosity and for daring to take chances without first carefully considering the consequences of their actions. If individuals make the wrong decisions when coping with conflict, they will engage in risky conduct and suffer long- and short-term consequences in a variety of physical and psychosocial health issues (Indonesia 2015). Unintended pregnancies and unsafe abortions, severe illness, STI/HIV infections, infertility, and even death are more frequent in young women as a result of unprotected sexual intercourse (Denno *et al.* 2015). The adolescent problems have an impact such is bad on adolescent reproductive well-being.

Reproductive health is a condition of physical, mental, and social well-being that is crucial for teenagers to comprehend, as it encompasses more than just sexual encounters. Due to a lack of appropriate information, adolescents seek and obtain knowledge about reproductive health from untrustworthy sources such as their friends or pornographic media. As a result, they have a distorted and unhealthy view of sex and reproductive health. Misperceptions about reproductive health and sexuality can also be carried over into their sexual behavior (Priohutomo 2018). Unplanned pregnancies at a young age, according to research, may predispose adolescents to poor health outcomes due to a lack of information. Unprotected

premarital sex, for example, can result in pregnancy complications, sexually transmitted diseases, and unsafe pregnancy termination (Okereke 2010).

Globally, 3 million young girls aged 15–19 have risky abortions each year, according to World Health Organization (WHO) estimates. Meanwhile, every year, 16 million girls aged 15 to 19 give birth, accounting for 11% of all deliveries (Organization WH 2014). Moreover, according to The Ministry of Health (2015) stated that about 33.3% of girls and 34.5% of boys aged 15–19 years started dating when they were not yet 15 years old. At that age, it is feared that teenagers do not have adequate life skills, so they have a risk of having premarital sex. In Central Java, roughly 1.9 percent of teenage guys and 0.4 percent of teenage girls have had sexual relations before to marriage (Indonesia 2015; Wijayanti & Nurpratama 2020).

The impact of youths people's risky sexual behavior on reproductive health, such as unwanted pregnancy (unwanted pregnancy). Unwanted pregnancy forces young people to choose between continuing the pregnancy and aborting it. Complications in pregnancy and childbirth are the leading cause of death among adolescent girls. Pregnancy complications and death are more common in young adolescents than in older women. The risk of death is highest at the age of under 15 years. Severe bleeding, infection, high blood pressure during pregnancy (pre-eclampsia and eclampsia), and unsafe abortion account for 80% of all maternal deaths (WHO 2015).

Psychological consequences are another impact of sexual behavior. The nature of pregnancy and childbirth puts young women in a tough spot. Young women who become pregnant, in the eyes of society, are a disgrace to their families and violate social and religious norms. This social judgment frequently pervades and is socialized within him. After learning about their pregnancy, students' feelings of confusion, anxiety, shame, and guilt are mixed with feelings of depression, pessimism about the future, which is sometimes accompanied by hatred and anger both towards themselves and their partners, and at fate, which causes physically healthy conditions, social, and mental aspects related to the reproductive system, function, and process of young people to be incomplete (Kasim 2014).

A person's tendency to behave sexually is influenced by attitudes, where the attitude itself is formed by a thorough knowledge of sex so that it can be said that the emergence of adolescents' intentions to carry out risky sexual behavior or not, in accordance with the knowledge and attitudes possessed (Rusmiati & Hastono 2015). The existence of this intention if supported by a normative environment will strengthen the emergence of consistent sexual behavior between knowledge, attitudes, and behavior. From the results of other studies, it was found that attitudes about sexuality that were not good had a higher risk of premarital sexual behavior, namely 4,525 times compared to good attitudes (Naja *et al.* 2017). Based on this phenomenon, the occurrence of sexual behavior in adolescents is influenced by several factors, and adolescent attitudes are one of the most significant opportunities for sexual behavior. This study aims to determine the factors that influence adolescent attitudes towards sexual behavior, this needs to be known to prevent the occurrence of sexual behavior problems among adolescents which have a considerable impact on reproductive and psychological health in adolescents.

2 METHODS

This is a quantitative method with an observational design and a cross-sectional approach. Specially, each research subject is only observed once between risk and effects (Atiglo & Biney 2018). The participants in this study were eighth-grade students at Bhakti Husada Brebes Vocational School. Purposive sampling was used to select research subjects, with the decision based on specific (subjective) considerations made by the researcher (Sastroasmoro 2011). The obtained sample size was 40 people. To determine, we used structured interviews and interview guidelines to collect data. the factors that influence adolescent attitudes

towards sexual behavior. All questionnaire data were analyzed using IBM SPSS Statistics 22.0 (IBM SPSS n.d.). Chi-square analysis is used in bivariate analysis to determine the relationship between each variable.

3 RESULTS AND DISCUSSION

This study was conducted at SMK Bhakti Husada Brebes in February 2021, with 40 respondents. The results of the research are as follows:

Table 1. Factors influencing adolescent sexual behavior attitudes.

No	Variable	Attitude			<i>P-value</i>
		Not enough	Good	Total	
1	Knowledge				<i>0.047</i>
	Poor	25 (80.6%)	6 (19.4%)	31 (100%)	
2	Excelent	4 (44.4%)	5 (55.6%)	9 (100%)	<i>0.123</i>
	Resources				
	School	12 (75%)	4 (25%)	16 (100%)	
3	Media	7 (53.8%)	6 (46.8%)	13 (100%)	<i>0.57</i>
	School, Media	10 (90.9%)	1 (9.1%)	11 (100%)	
4	History of sex				<i>0.025</i>
	Ever	9 (75%)	3 (25%)	12 (100%)	
5	Never	20 (71.4%)	8 (28.6%)	28 (100%)	<i>0.038</i>
	The role of parents				
6	Poor	17 (89.5%)	2 (10.5%)	19 (100%)	<i>0.025</i>
	Excelent	12 (57.1%)	9 (42.9%)	21 (100%)	
7	Sexual behavior				<i>0.038</i>
	Negatif	16 (88.9%)	2 (11.1%)	18 (100%)	
	Positif	13 (59.1%)	9 (40.9%)	21 (100%)	

Based on Table 1 The following factors influence adolescent attitudes toward sexual behavior: knowledge factors, information sources, history of sexual relations, parental roles, and sexual behavior. The following are the results of the bivariate test with the Chi-square test: The knowledge cause has a p value of 0.047, indicating that there is a link between knowledge and adolescent attitudes toward sexual behavior. The reason for the source of information has a p value of 0.123, indicating that there is no relationship between the source of information and adolescent attitudes toward sexual behavior. The history of sexual relations showed that the p = 0.570, meaning that there was no relationship between the history of sexual relations and adolescent attitudes towards sexual behavior. The parental role reason has a p = 0.025, implying that there is a link between parental role and adolescents' attitudes toward sexual behavior. The P-value for the sexual behavior reason is 0.038, indicating that there is a relationship between sexual behavior and adolescent attitudes toward sexual behavior.

3.1 Knowledge factors on adolescent attitudes

Based on Table 1 shows the factors that influence adolescent attitudes toward sexual behavior, including the knowledge factor; the chi-square test results show a relationship between knowledge and adolescent attitudes toward sexual behavior, this is by the results of earlier research conducted by Kadek Putri (2014) which stated that respondents who were

well-informed were respondents who had a positive attitude towards avoiding premarital sexual behavior and respondents who had a negative attitude towards premarital sexual behavior. The analysis test results revealed a significant relationship between knowledge and attitudes toward premarital sexual behavior (Juliani *et al.* 2014). Based on the results of the study, it can be concluded that knowledge can affect each attitude towards premarital sexual behavior. Because knowledge is one of the important factors in shaping the attitude of a teenager who enters the transition period. Knowledge can also change a person's perception of sexuality.

The analyses of a separate study by A. Hastari (2019) besides which, there is a link between knowledge and risky sexual behavior; adolescents with less knowledge are 3,764 times more likely to engage in sexual behavior than adolescents with good knowledge (Ashari *et al.* 2019). The attitude of adolescent sexual behavior is not only determined by the level of sexual knowledge but is more determined by their psychosocial maturity so that adolescents can decide what is best for themselves and are not easily influenced by their environment. Someone who has good knowledge but is not supported by good interests, desires, will, and motivation, then the attitude towards his behavior can be bad. Likewise, with someone who is less knowledgeable, they may have good will and motivation so that their behavior can become good.

3.2 *Factors source of information on adolescent attitudes*

Besides which, there is a link between knowledge and risky sexual behavior; adolescents with less knowledge are 3,764 times more likely to engage in sexual behavior than adolescents with good knowledge. The findings of the 2012 IDHS (Indonesian Demographic and Health Survey) According to the poll, male adolescents aged 15 to 19 preferred sources of reproductive health knowledge from peers and instructors, while female adolescents preferred sources of reproductive health information from moms (parents), teachers, and health workers (Jasny *et al.* 2019; Statistik & Nasional 2012). This is consistent with other studies' findings, which show that schools may be used to give teenage reproductive health education and that instructors play an essential role (Fitriana & Siswantara 2018). Although the potential of teachers as a source of reproductive health information for adolescents is great, their role is not yet optimal. This is as indicated in the results of research conducted on high school teachers in Semarang City that although teachers have a good perception of reproductive health education, teachers are still reluctant and taboo when teaching sex education (Juariah 2020; Pawestri 2011).

Based on Table 1 The factors that influence adolescent sexual behavior attitudes can be seen. Based on the findings of an earlier study conducted by Aminatussyadiah (2020), teenagers who accessed the most media were those who watched the news at least once a week. The results of the analysis test showed $p = 0.000$ so that television media had a big impact in increasing teenage pregnancies (Ayu Aminatussyadiah *et al.* 2020). Information media has a significant contribution in introducing sexual content to teenagers. Both through movies, games, and pictures that have pornographic content. In addition, there are also many soap operas broadcast on television that can plunge teenagers into negative activities. This kind of spectacle can cause curiosity in teenagers to try to do something that smells of sexuality, from hugging, kissing each other to having sex. Thus, the researcher's response to the results of this study is that the type of information source greatly influences adolescent attitudes in sexual behavior, and sources of information through the media have a greater role in sexual behavior in adolescents than through school.

This is by the results of research conducted by Lou (2012) which states that the use of media and the messages presented are factors that influence knowledge, attitudes, and behavior related to sex in adolescents (Lou *et al.* 2012). Sexual behavior among teenagers is because teenagers are accustomed to using digital technology through their cell phones (Fevriasanty *et al.* 2021).

3.3 *Factors history of sexual relations on adolescent attitudes*

Based on Table 1 shows the factors that influence adolescent attitudes towards sexual behavior, including the history of sexual relations, based on the results of the study, respondents with a history of sexual intercourse had a bad attitude, the results of the analysis show this means that there is no relationship between the history of sexual relations with adolescents' attitudes towards sexual behavior. Results of a previous study showed that male are not a problem if having sex before marriage compared to female adolescents. Furthermore, the percentage of male teenagers who claimed to have had premarital sex was higher than female (7.3 percent and 2.3 percent) The results of further analysis indicate that, adolescents who have ever dated had a chance 14.120 times having premarital sex compared to them who have never dated (Oktriyanto & Alfiasari 2019).

The results of research conducted by Fitri (2014) said that adolescent knowledge related to reproductive health was still lacking, even though many programs related to reproductive health were already running. A strong sense of curiosity is the basis for teenagers to carry out risky behavior with relationships outside of marriage. Besides that, peers have a big influence on the lives of teenagers. This is also proven based on IDHS (Indonesian Demographic and Health Survey) data (2012) about the percentage of discussions carried out by adolescents related to reproductive health that is mostly carried out with their peers (Mediastuti 2014; Statistik & Nasional 2012).

According to the findings of Rosdarni's (2015) study, teenagers with a positive attitude have 1.5 times the chance to engage in dangerous premarital sexual behavior than adolescents with a negative attitude. Teenagers' permissive attitude towards premarital sexual behavior is caused by teenagers' assessment that premarital sexual behavior is something that is natural to do, such as kissing to having sexual relations as long as teenagers love each other. This is by the theory explained by Bandura (2011) that during adolescence there are major changes physically, mentally, and socially and at this time several patterns of behavior begin to form, such as self-identity, sexual maturity, and the courage to carry out risky behavior (Rosdarni *et al.* 2015).

3.4 *Factors the role of parents on adolescent attitudes*

Based on Table 1 shows a factor that affect adolescent attitudes toward sexual activity, including the role of parents; based on the report's results, most of the roles of parents who do not have a positive attitude as well. Based on the findings of the study, there is a link between parental role and adolescent attitudes toward sexual behavior. This is in accordance with previous research, which found that adolescents who had infrequent communication with their parents about sexuality had 1.4 times the chance of engaging in risky premarital sexual behavior as adolescents who communicated frequently. The discomfort or reluctance of parents and adolescents to discuss sexuality contributes to a lack of communication between adolescents and parents when discussing sexuality (Rosdarni *et al.* 2015).

The family has a very important role in providing information about puberty in adolescents. Parents can facilitate by actively asking about every change experienced by adolescents in every development during puberty (Ramadhani *et al.* 2019).

This is by the results of research conducted by Haryani (2017) which states that there is a relationship between family support and behavior to prevent early pregnancy and the value of OR = 3,128, adolescent girls with family support who have supported have 3,128 times the opportunity to behave in preventing pregnancy. compared to adolescent girls who do not have support from their families (Samsudin 2020). The existence of parental attention or control over children can delay teenagers having sex, this is because between

parents and children there is an intensive relationship or communication that allows discussion, sharing and problem solving together.

Based on the results of the study, the researcher's response was that the better the support or the role of parents in adolescents for preventing teenage pregnancy, the attitudes of adolescents towards sexual behavior to prevent pregnancy were getting better. And if the parental support for adolescent girls is getting worse about preventing pregnancy, then the attitude towards sexual behavior for preventing pregnancy in adolescents is getting worse.

3.5 *Factors of sexual behavior on adolescent attitudes*

Based on Table 1 shows the factors that influence adolescent attitudes towards sexual behavior including pregnancy prevention behavior factors. There is a relationship between pregnancy prevention behavior and adolescent attitudes towards sexual behavior. This is by the results of other studies which say that attitudes towards sexuality are the most dominant factor influencing and predicting premarital sexual behavior in students. Respondents whose attitudes towards sexuality are more permissive have a 4 times greater risk or tendency to engage in sexual behavior at risk of adverse events compared to respondents who are less permissive. This is because direct or indirect encouragement from close friends to have premarital sex causes a person to be permissive and allows them to do so (Azinar 2013).

This is supported by the results of earlier research conducted by R. Haryani (2017) which states that there is a relationship between attitudes and behavior to prevent pregnancy at an early age, and the OR value = 16.9 adolescent girls with a positive attitude have a 16.9 times chance to behave to prevent pregnancy at an early age compared to adolescent girls with a negative attitude (Haryani 2016).

Attitude is a predisposition (determinant) that gives rise to attitude-based behavior. Attitude develops from knowledge that is perceived as good (positive) or bad (negative), which is then internalized into him (Dalimunthe 2013). This is also by L. Green's theory states that the predisposing cause, in this case, is an attitude related to a person's behavior, and Attitude is defined as a person's reaction or response to an object, which then influences personal behavior toward the object in specific ways (Azwar 2010; Yolanda *et al.* 2019).

This research was attempted and carried out in accordance with scientific procedures, but it still has limitations, including the following: the factors that influence adolescent attitudes toward sexual behavior are still very limited, while there are many other factors that influence adolescent attitudes toward sexual behavior. There is a limitation to questionnaire research in that respondents provide answers based on the available answer choices, while there is wealth of data that should be investigated to evaluate the factors that influence attitudes toward sexual behavior.

4 CONCLUSION

Based on the according to findings, the factors that were strongly related to adolescent attitudes toward sexual behavior included: knowledge, parental roles, and behavior. While the source of information and history of sexual intercourse showed no significant relationship. It is hoped that by understanding the factors affecting adolescent attitudes toward sexual behavior, the findings of this study will serve as the first step for the education and health sectors in avoiding and reducing the impact of sexual behavior on adolescents. The significance of educating adolescents about the negative consequences of their social media exposure to sexual attitudes and behavior, as well as the role of parents in supervising the restriction of access to sexual media and increasing communication between parents and children about adolescent reproductive health issues. Future research requires a larger number of samples and in-depth interviews with adolescents are needed to decide the attitudes of adolescents in sexual behavior.

ACKNOWLEDGMENTS

Thank you to the Harapan Bersama Polytechnic for supporting this research. Thanks, are also conveyed to the Principal of SMK Bhakti Husada Brebes who has given permission to conduct research and students who are ready to take part as respondents in this study, rotary evaporators, uv-vis spectrophotometry.

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Challenges and support of community health nurses in the implementation of Non-Communicable Disease (NCD) health promotion: A qualitative study

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ABSTRACT: The increasing prevalence and low understanding of risk factors for non-communicable diseases (NCD) are the focus of implementing health promotion to the community. The task of community nurses is to provide health promotion to the community, one of which is the topic of non-communicable diseases. Health promotion requires support from various stakeholders because nurses get several challenges during the implementation. This study aims to determine the challenges and support of community health nurses in the implementation of NCD health promotion. This study used a qualitative-descriptive phenomenology study with a total of 16 nurses from the community health centre. The sampling technique used was purposive sampling. Data analysis used the Colaizzi approach. The results of the study showed several challenges and support in implementing NCD' health promotion, including (1) Challenges of the paradigm of health service utilization, (2) Challenges of workload from the main task, (3) The existence of high commitment, and (4) The existence of good management. The challenges and support illustrate that the importance of participation from community, stakeholders, and colleagues in the implementation of NCD health promotion.

1 INTRODUCTION

Non-communicable diseases are still the leading cause of death in the world. Every year, as many as 41 million people die from heart attacks, stroke, cancer, chronic respiratory disease, diabetes, or mental illness (World Health Organization (WHO) 2020). The problem of non-communicable diseases has an impact on social conditions and affects the economy. The results of the WHO report explain that if a country has an exemplary implementation in overcoming the problem of non-communicable diseases, then a country will save 10 million people living in 2025 and prevent 17 million people from stroke and heart attack in 2030 (World Health Organization (WHO) 2020). Primary level services have a significant role in implementing health promotion to prevent deaths from NCDs.

Health promotion is a process to improve the health control of everyone (Istifada *et al.* 2021). Implementing promotive and preventive efforts is one of the strategies formulated in the Sustainable Development Goals (SDGs). One of the targets for adequate universal health coverage (UHC) is strengthening health services to prevent and control NCDs (United Nations World Commission on Environment and Development 2017). Community nurses are one of the health workers at the forefront of public health services (Rodén *et al.* 2015). Nurses working in primary care can increase the effectiveness of disease prevention and health promotion (Keleher & Parker 2013).

The nurse explained that the various challenges and support faced came from external (community) and internal factors (availability of community health center resources). The nurses' experience in Casey's research describes that participation from the community is the best support in implementing health promotion and prevention (Casey 2007a). Previous research has explained the importance of the support given to nurses to carry out prevention

and health promotion in schools (Banfield *et al.* 2015). Based on this phenomenon, it is necessary to discuss the new perception about challenges and support for nurses during health promotion regarding NCD. It aims to describe nurses' experience and become a reference for stakeholders in determining and identifying the needs of nurses during the health promotion process.

2 METHOD

This research uses a qualitative study with a descriptive-phenomenological approach. Implementing health promotion efforts in Indonesia is a complex phenomenon, so this is the justification for describing it using qualitative methods. Complex problems are the characteristics of research using a qualitative method approach (Creswell 2007). The number of participants consisted of 11 nurses who worked at the community health center. The inclusion criteria of this study were (a) working in a community health center for at least the last six months; (b) having experience working in individual, family, and community services at a community health center. Selecting participants used a purposive sampling technique with sample selection by the research objectives. The data collection method used semi-structured in-depth interviews and open-ended questions to explore nurses' experiences (Table 1). The interview process was carried out for 30–45 minutes/participant using a voice recorder. The data analysis process uses the Colaizzi approach. These data are valid and meet the criteria of credibility, dependability, confirmability, and transferability. This research was conducted in 2020 and had been ethically permitted with the approval of the Ethics Committee of the Faculty of Nursing, University of Indonesia (No.49/UN2.F12. D/HKP.02.04/2019). This ethical process is carried out by considering benefits, non-maleficence, fairness, and statements of consent from participants.

Table 1. Question script.

Please describe the challenges you felt during the implementation of health promotion at the community health center
Please describe the support you have during the implementation of health promotion at the community health center

3 RESULT

3.1 [Theme 1] Challenges of the health service utilization paradigm

3.1.1 Community participation in promotive and preventive services

The challenges of nurses in implementing health promotion and prevention of NCDs include the paradigm of using health services, many workloads outside of the main task, and limited capabilities and facilities. Some challenges come from the community regarding the paradigm of health service utilization, such as the lack of community participation in promotive and preventive services and the high motivation of the community in curative services. Lack of public attention in participating in promotive and preventive services.

“Considering that the past wind was . . . Some were distracting, some were indifferent” (P9)

The low participation is also shown by the reluctance of the community to attend UKBM services.

“People think ... lazy to come, why just sit down” (P7)

Some people are not enthusiastic about understanding health information. People often claim to understand when the question-and-answer session begins, but many cannot answer the questions during the evaluation.

3.1.2 *Community motivation on curative health services*

The high motivation of the community for curative services, so that most of the people who come to the community health center are sick patients.

“The paradigm of today’s society is like this, I am sick, ma’am, I need medicine” (P5)

The absence of treatment at UKBM services causes low community participation in community health services.

“What are they, they need medicine, if there’s a lot of medicine, there will definitely be a lot of people coming...” (P4)

3.2 *[Theme 2] Workload challenges outside of main tasks*

3.2.1 *Have primary duties*

In addition to duties related to the profession, nurses have additional duties outside of the main task. For example, limited human resources cause health workers to be responsible for two or more programs.

“I also have a program apart from nurses... Like asset treasurer... registration room, guard the pharmacy room, if there’s no one there, we have to change that all...” (P3)

Less than the optimal implementation of health promotion and prevention of NCD is sometimes caused by nurses getting sudden assignments or shifting assignments.

“We like there is training, some are DL (foreign service), some are shifts...”

3.2.2 *Domination carrying out curative tasks*

The number of curative tasks in the building causes the workload to increase. This condition makes it difficult for nurses to complete their primary task, namely preparing nursing care.

“The nurse’s job is basically to make health care services, sometimes they are neglected ... they (doctors) order hecting” (P13)

The density of work completed inside the building often causes fatigue to continue tasks outside the building.

“The visits are not effective ... Because we are in the morning until 11 am until 12, sometimes we have to really stay in the building” (P15)

3.3 *[Theme 3]: High commitment support*

3.3.1 *Stakeholder participation*

Nurses also need high commitment from various parties, which is indicated by the active participation of stakeholder and the willingness of nurses to share experiences. Stakeholders come from internal health offices and should also be involved in regulation.

“If only the community health officers work alone, it means that it will not work without stakeholders” (P10)

The participation of the head of the community health center in out-of-building services is the support needed by nurses. In addition, the community health center knows the condition of the area and its people.

“The head of the community health center must know, must see the field conditions” (P13)

3.3.2 *Sharing experiences with colleagues*

In addition to commitment from stakeholders, willingness among colleagues to share experiences is an important thing needed.

“I still have a lot to learn from friends who are already advanced here, especially for the field . . . ” (P9)

3.4 *[Theme 4]: Good management support*

3.4.1 *The existence of performance monitoring*

The successful implementation of health promotion and prevention of NCD cannot be separated from good management, such as monitoring and evaluation (money) of performance and clarity of responsibilities. Therefore, the input from the head of the community health center during money is part of the needed support.

“See how our efforts are to carry out our main tasks, so the term is that there is feedback” (P14)

In addition, one of the nurses needed support to carry out money to the cadres.

“Discussion with the cadre about what he got from the training, so I know that too . . . ” (P4)

3.4.2 *Clarity of responsibilities*

Good management is indicated by the clarity of the responsibilities of each health worker. This strategy requires the firmness of the head of the community health center as a stakeholder. If the head of the community health center has the control to divide the roles and duties of each staff, then the resources are optimally absorbed.

“If actually all of us can use (re: use of human resources), we all can do this together” (P16)

The central nurses hoped that there would be support for contract staff to be included in services outside the building (community health service).

“Not only did I go down, but my outsourcing friends (BLUD nurses) went to the field” (P9)

4 DISCUSSION

4.1 *[Theme 1] Challenges of the health service utilization paradigm*

The nurse explained that the low participation and motivation of the community in promote and preventive services caused the health information provided not to have an impact on the expected changes. Meanwhile, nurses' experience in Casey's study describes that participation from the community is the best support in implementing health promotion and prevention (Casey 2007b). If there is a lack of community participation and motivation, it will not achieve the expected target after implementing health promotion and prevention.

The experience of most participants explained that people often do not pay attention to health workers when providing education at community health services. Providing the right place and method can increase the effectiveness of implementing health promotion (Berman *et al.* 2016). In addition, the concept of health promotion model explains that the success of implementing health promotion is influenced by the individual's desire to improve or optimize his health (Pender *et al.* 2015). Therefore, nurses perceive this as one of the obstacles in implementing health promotion and prevention of NCD. Nurses should prioritize the implementation of health promotion in people who have motivation first (Brobeck &

Odenchrants 2013). It shows the importance of people's attention and motivation for creating a paradigm shift from illness to a paradigm of health.

Some other nurses explained that the paradigm challenge occurred because many people were still oriented towards curative services, compared to promotive and preventive services. The first thing nurses get is people who already have health problems and symptoms of an unhealthy lifestyle (Brobeck & Odenchrants 2013). It causes nurses to carry out more health education for people who have been diagnosed with illness/sick people. Community nurses ideally carry out health education at the primary prevention level or when the community is in good health (Allender *et al.* 2015).

Implementation of education at the primary level is sometimes difficult to implement, and this allows nurses to carry out education at the secondary and tertiary prevention levels (Allender *et al.* 2015). Services at the secondary prevention level are carried out to restore function to optimal and prevent complications/disability (McEwen & Pullis 2018). Therefore, the participants of this study also admitted that health education was mainly carried out when the community came for routine medical visits at the community health center. Community participation in self-care is more dominant in access to treatment than healthy living behaviour (Casey 2007a). It can be overcome if the community changes the orientation of the previously curative paradigm to promotive and preventive. It follows the concept of elements of successful health promotion, namely (a) the importance of client/community commitment to self-care, (b) being willing to participate in promotive and preventive efforts (Maijala *et al.* 2016).

4.2 [Theme 2] Workload challenges outside of main tasks

High workload affects the level of fatigue felt by nurses (Hariyono *et al.* 2009). In addition, most participants explained that they often experience difficulties in carrying out promotive and preventive services due to the many curative services tasks and the various tasks assigned to them. This condition causes time constraints when performing promotive and preventive services. The results of this study are similar to the experience of various studies; their role is to prioritize curative services (treatment), thus causing time constraints when carrying out promotive and preventive services (Casey 2007a; Hariyono *et al.* 2009; Pender *et al.* 2015; Wilhelmsson & Lindberg 2009).

One of the nurses explained that she was still getting a night shift schedule (night watch). Shifting work with a high load can lead to ineffective communication with colleagues, family, and others. It can overcome this condition if the management function that focuses on human resources goes well (Aldossary *et al.* 2013). The running of the workforce function in community health center management can make the distribution of resources balanced, competent, and mutually supportive (Marquis & Huston 2012). Suppose the community health center pays attention to the ratio of health workers to implementing promotive/preventive/curative services. Nurses need time to carry out health promotion and prevention because reaching healthy communities requires time allocation for health promotion activities (Brobeck & Odenchrants 2013). Time constraints could lead to nurses' neglect of promotive and preventive implementation (DeCola *et al.* 2012).

4.3 [Theme 3] High commitment support

Patients with chronic diseases are vulnerable populations who need care from the community and government nurses (Allender *et al.* 2015). Stakeholder support needed is from internal health centers and commitment support from regional government officials around the community health center. As a result, this becomes an obstacle. In addition to making agreements with stakeholders, their high commitment is part of the support needed by nurses. The implementation is carried out well if there is commitment support from the government in establishing regional regulations (Wilhelmsson & Lindberg 2009).

The other most crucial thing relates to the commitment of stakeholders, the need for participation from the head of the community health center as the highest stakeholder in the community

health center in implementing promotive and preventive efforts. The importance of support from leaders and colleagues in the decision-making process on the implementation of health promotion (Furunes *et al.* 2018). If all parties participate, then the program of activities will be easier to manage, resulting in achieving targets (Furunes *et al.* 2018). In addition to the participation of stakeholders, nurses also need commitment from colleagues to share their experiences. Sharing experiences with colleagues can increase motivation and self-efficacy in health promotion (Furunes *et al.* 2018). One of the junior nurses conveyed the need for knowledge from experienced senior colleagues (span of work > 3 years). Social network-based discussions can be an alternative method for nurses to coordinate and share knowledge (Nurrahima 2017). Therefore, this condition can be used as a solution for nurses to overcome the difficulty of conducting face-to-face meetings to share knowledge or experiences. Knowledge-sharing activities are part of the elements of successful implementation of promotive and preventive efforts (Maijala *et al.* 2016).

4.4 [Theme 4] Good management

Another support nurses need creating good management in the community health center environment. Good management is indicated by the existence of monitoring and evaluation of performance and clarity of roles and responsibilities of each nurse. A leader should listen, show concern, and provide feedback to his staff (DeCola *et al.* 2012; Pender *et al.* 2015). The feedback on the promotive and preventive efforts is an assessment of the development of her competence. The form of feedback is related to the skills/competencies possessed, as well as the ability of nurses to face new challenges in daily tasks (Pool *et al.* 2015). Therefore, to provide this feedback, the leader must know the progress of his staff by monitoring and evaluating. Lack of management support can cause the implementation of promotive and preventive efforts not to be prioritized (Brobeck & Odencrants 2013).

Leaders must also know the potential of their staff so that the division of tasks and roles of each health worker is utilized optimally. Therefore, the clarity of the responsibilities of each nurse confirmed by the community health center leadership is a form of expected management support. Leaders must know their staff's potential to build organizational capacity (Eriksson *et al.* 2010). Therefore, the existence of a leader's role in knowing the potential of his staff can create clarity of responsibilities of each staff. It is done so that the resources at the community health center are well-absorbed so that limited human resources do not interfere with implementing promotive and preventive efforts.

5 CONCLUSION

Based on the research conducted, nurses have challenges in implementing health promotion and prevention of NCD. These challenges include the paradigm of the utilization of health services, the enormous workload of nurses outside of their primary duties, and limited capabilities and advice. Therefore, nurses need support from various parties to face the challenges they are going through. The support needed in implementing health promotion and prevention of NCD includes high commitment, and good management. The recommendation is by setting a cadre training budget, appreciating health cadres, and procure supporting facilities to implement promotive and preventive efforts successfully. In addition, it is necessary to increase the capacity of health workers in promotive and preventive efforts by considering the implementation of training (communication training in advocating and service excellent training) and providing opportunities for nurses to continue nursing professional education.

ACKNOWLEDGMENTS

I would like to thank the Faculty of Health Sciences, Undergraduate Study Program and Nursing Profession, Universitas Muhammadiyah Tangerang. This work supported by

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Qualitative study: Mother's coping in care of low birth weight baby

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ABSTRACT: Mothers who have LBW babies need an adaptation process in caring for their babies. Mothers who are not emotionally ready to take care of their babies can cause low birth weight babies to be hospitalized again. The purpose of this study was to determine the mother's coping in caring for LBW infants. This research was conducted at the Muhammadiyah Hospital of Tegal. Informant of this study were postpartum mothers who had LBW babies as many as 6–10 people. The method used in this research is qualitative with a case study approach. The results of this study obtained 3 themes, namely maternal coping mechanisms, positive and negative coping responses. The system from the family and health workers is needed by mothers in caring for LBW babies.

1 INTRODUCTION

The Infant Mortality Rate (IMR) is an indicator used to show the state of health status in a community, including maternal and infant services (Central Java Statistics Agency 2019). As many as 7000 babies born in the world die every day, while in Indonesia the neonatal mortality rate is 15 per 1000 live births (World Health Organization (WHO) 2018). indicators that can be used as a benchmark for infant health, such as predicting the risk of child health, growth, and future development of children, and the possibility of survival is by knowing the weight of the newborn (Jayant *et al.* 2011). Low Birth Weight (LBW) babies are 20 times more likely to experience complications and die compared to babies born with normal weight. LBW has a risk of cognitive deficits, motor delays, cerebral palsy, disorders of the respiratory system, central nervous system, cardiovascular, hematology, gastrointestinal, kidney, thermoregulation and behavioral problems (Chang *et al.* 2015; Mathewson *et al.* 2017). Babies born small require special handling so that their growth is not stunted or known as stunting (Benson Atitwa 2015). Low birth weight (LBW) is one of the main risk factors for stunting in toddlers. The first 1000 days of life is a critical period of child development, starting from the time of conception to postpartum this is determined by the maturation of the metabolism that affects the growth and development of the child. If infection problems occur or are less than optimal, the child's growth can be disrupted, causing poor nutrition, which can manifest as or as malnutrition (Robertson *et al.* 2019). WHO states that 15% to 20% of all births worldwide are LBW babies. The prevalence of LBW varies between regions with the highest 28% in South Asia and the lowest 6% in East Asia and the Pacific region. In Indonesia, LBW is the main cause of neonatal mortality, which is 7150 births or 35%. In Central Java, LBW cases were 24% (Darmawan 2019). The percentage of LBW in Tegal district was 7.36% (Tegal District Health Office 2018). Interventions to reduce malnutrition and prevent prematurity and LBW are to encourage early stimulation for optimal development (Ahishakiye *et al.* 2019). Mother's knowledge regarding optimal care for LBW can be increased through educational practices, discussions, and the use of technology as a learning medium as a way to prevent the impact of stunting as

an effort to increase mother's knowledge and confidence in caring for LBW (Rustina & Efendi 1907). Research This is important because identifying the care needs of LBW babies will produce comprehensive LBW care information. Care of LBW babies by mothers and their families so as to reduce the risk of LBW babies experiencing stunting and other complications. The advantage of this research is that it uses a qualitative method, so that this research can in-depth know the care of LBW babies at home. In addition, research on similar topics using qualitative methods is still very rarely done. The purpose of this study was to determine the mother's coping in caring for LBW infants.

2 METHODS

This research was conducted at Muhammadiyah Hospital Tegal. The consideration of researchers choosing the research location is because it is a hospital that has a fairly large number of LBW babies, which is 30 patients every month. The form of in-depth interview questions includes several parts, namely how to cope with mothers in caring for LBW babies. The method used in this research is qualitative with a case study design. This research uses informants of mothers and families who have LBW babies as many as 6–8 people. The data in this study were obtained through in-depth interviews with informants, both main informants and supporting informants. The main informants in this study were postpartum mothers, while the supporting informants came from families and nurses. Determination of informants in this study was done through purposive sampling technique. In-depth interviews were conducted using an interview guide instrument and a voicer. In addition, researchers also prepared cameras and stationery to document activities during data collection. Data analysis was carried out using this method using Colaizzi. The validity of the data in this study was carried out through source triangulation and member checking methods. Source triangulation is carried out by conducting interviews from the main informant's data sources and supporting informants, while member checking.

3 RESULTS

Based on the results of the study, various themes were obtained, namely maternal coping in caring for LBW infants, namely maternal coping mechanisms, positive, and negative coping responses.

3.1 *Coping mechanism*

The coping mechanism is done by praying, support from family Support and family support such as giving enthusiasm, attention, much needed by mothers in caring for LBW babies as stated by several participants below.

- “From the family, they provide support by telling them to be patient, which is important to be healthy like other children” P6
- “You have to be patient, don't be pessimistic, jealous or anything, lots of prayers, take care of it quickly” P7
- “Mothers need mental support if they can take care of LBW babies, from their families and mothers” P4 The support from the family is to pray together for a healthy baby to be like other babies” P2
- “At the very least, the mother's husband's family support gives encouragement to her mother, if she eats or whatever, so that her mother doesn't take care of her baby, she's happy, so educate the family so that it doesn't burden her mother's mind (usually this is what she is told to do)” P1 2.

3.2 Positive coping

Mothers who are experienced in caring for LBW babies are prepared to take care of LBW babies as stated by the following participants:

- “I always give enthusiasm, yes, the child’s condition like this is a little input because it mainly takes care of health, My child gives nutritious food, wants to go for 7 months, the important thing is fish and milk vegetables, I only take a bath weighing 3.5 kg if the weight is stiff, I can’t stand it wind” P8 3.

3.3 Negative coping

At first, I was sad because my child is LBW, I have tried to eat nutritious food but my child is small, at first, I did not pay attention to my child P3.

4 DISCUSSION

The postpartum period is considered a sensitive period in which mothers are more susceptible to psychological stress states that small and sick newborns may require additional follow-up to assess recovery, feeding, and weight. maintain temperature, breastfeed well and the mother is confident in caring for her baby (WHO 2020). Parents and caregivers should be educated and taught to build their confidence in caring for their babies at home. Research by Lee et al shows that mothers with low birth weight babies have several emotional changes in the care of their babies starting from the beginning of changes in parenting methods, forming an intimate mother-child bond and worries and expectations about child development (Lee et al. 2019). This shows that a follow-up program with early intervention is needed to increase mother’s confidence in child-rearing skills and can increase mother’s attachment and quality of family life with LBW. Maternal knowledge is part of the adaptation process and coping (Obtaining information on the infants and their treatment would promote maternal knowledge and coping skills) (Altimier, Leslie 2007). However, several studies reported that parents’ need for information and knowledge was not met during the hospitalization of their newborn (Hasanpour et al. 2017). Mothers who are not able to acquire sufficient knowledge about the infant’s condition may have a delayed attachment process with their infant. Lack of information about infant care can cause stress, contributing to poor maternal coping strategies for low birth weight (LBW) infants. This study aims to examine the relationship between knowledge of LBW infants on care and maternal coping strategies. coping strategies, implying that increasing knowledge and decreasing stress levels will improve maternal coping. Therefore, it is recommended that nurses equip mothers and families to be active and proactive learning opportunities through health education programs on infant care (Tambunan et al. 2020).

5 CONCLUSION

LBW babies require additional attention and care while being cared for at home to minimize the risk to the baby’s health. Increased attention to keeping LBW babies warm additional support for breastfeeding and monitoring the growth and development of babies paying attention to mothers and babies can optimize mothers who care for LBW babies.

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Nurses' perceptions regarding the impact of natural disasters

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ABSTRACT: Nurses are professionals engaged in the health sector. In addition, nurses can also be involved in natural disasters to reduce their impact. The impacts that arise can be in the form of physical and psychological impacts on the survivors. The purpose of this study is to understand more deeply the impact of disasters from the perspective of nurses who are tasked with assisting disaster survivors in Indonesia. This study adopted a qualitative descriptive design to dig deeper into nurses' perceptions regarding the impact of natural disasters. Fourteen nurses who had volunteered in disaster areas participated in this study. Nurses were interviewed, then the data were transcribed and analyzed thematically. Two main themes identified in this study include (1) the negative impact of physical, psychological, and material losses after a natural disaster and (2) the positive psychological, social, lifestyle, and spiritual impact of a post-natural disaster. The findings of this study confirm previous research that many nurses know the negative impact of natural disasters and some know the positive impacts that arise after natural disasters occur. This study also shows that few nurses know and understand the positive impact after natural disasters occur. Therefore, Indonesian nurses who volunteer in natural disasters need a lot of training to assist survivors, especially to foster positive impacts after natural disasters.

1 INTRODUCTION

Natural disasters that occur significantly in the world will have an impact on individuals, families, communities, and the environment. The impact of the disaster can be detrimental both materially, physically, and psychologically Al Khalailah *et al.* (2012). In 2017, the Center for Research on the Epidemiology of Disaster (CRED) noted that 335 natural disasters affected the lives of more than 95.6 million people, killed more than 9,697 people, and cost a total of US\$335 billion. While in Indonesia during 2018 there were 1,233 incidents of natural disasters and human disasters (Sattler *et al.* 2018). Psychological losses are experienced by the community after natural disasters such as post-traumatic stress disorder (PTSD) (Adams & Boscarino 2006; Galea *et al.* 2005). PTSD is a psychiatric disorder that occurs in someone who has experienced or seen traumatic events such as natural disasters, accidents, terrorism, war, rape, or other violent behavior (Moeller *et al.* 2001). The impact of disasters other than PTSD as a form of negative response to a trauma event will lead to a positive response, namely posttraumatic growth (PTG). PTG is a form of positive change from past experiences that occurs as a result of the struggle to live through a traumatic event that can be due to a chronic illness, war, disaster, rape, and other traumatic events (Tedeschi & Calhoun 2004). The response that appears in each person is different, whether it is a negative or positive response from individuals who have experienced trauma.

A person who experiences PTG after a traumatic event is different for each person. The growth and adaptation of individuals after a disaster or other traumatic event depends on their mental health (Blackie et al. 2017; Jayawickreme et al. 2015). Several surveys reported for the incidence of PTG as many as 83% of individuals who survived life-threatening diseases, natural disasters and wars reported at least one positive change in themselves (Fan et al. 2017; Li et al. 2015). Individuals with good self-restraint need a short time to live again and conversely individuals with poor coping will take a longer time to resolve the impact of a traumatic event.

The time it takes for individuals who experience PTG is influenced by mentality, age and gender. Changes in self related to stress and traumatic events, especially positive psychological views will stick after 6 months (Jeon et al. 2017; Wijoyo et al. 2020). For example, the process of changing PTG after the earthquake in Wenchuan, China, it was found that female sex was more common than male (Meng et al. 2018). The impact of natural disasters will result in traumatic events for some individuals. If this is not taken seriously, it will have a bigger impact. This prevention requires that everyone is trained to work together in managing post-disaster situations, especially health workers.

Natural disaster management actions can be carried out by health professionals to prevent a greater psychological impact. The health team, especially nurses, is one of the professions prepared for disaster conditions (Emery 2009; Pourvakhshoori et al. 2017). Nurses are a group of health professionals who are expected to be involved with disaster response and rehabilitation, given their workplaces such as hospitals or communities (Al Thobaity et al. 2015). Nurses who will be sent to disaster areas must be prepared carefully to provide proper health services.

Nurses are one of the groups of health workers who are expected to be involved in handling and mitigating the impact of disasters because this profession is related to hospitals or communities. Nurses who live in remote areas and far from access to health services do not have many choices in the disaster management process. So that nurses in remote and disaster-prone areas will take actions that nurses only know about (Kulig et al. 2017). This results in different perceptions or views on each nurse sent to or handling natural disasters.

Nurses' perceptions regarding the handling of natural disasters are very diverse. Studies conducted regarding nurses' perceptions of disaster preparation concluded that nurses who faced disasters would have difficulty if they were not prepared ahead of time (Wenji et al. 2015) Nurses' perceptions that arise regarding disaster management are influenced by experience, education, and curriculum introduction during nurse education and areas affected by disasters.

Based on the explanation above, the researcher is interested in researching the perception of nurses in dealing with the impact of natural disasters. This research was conducted with a descriptive qualitative research type. Qualitative research by conducting in-depth interviews with participants, especially nurses who fit the research inclusion criteria to get an in-depth picture related to the impact of post-natural disasters.

2 METHODS

This study uses qualitative research methods with a qualitative descriptive approach. Qualitative descriptive research is research whose findings are closer to the data (Sandelowski 2010). According to Doody & Bailey, the purpose of qualitative descriptive research is not aimed at describing the essence or important structure of an experience that focuses on what is important and meaningful as in descriptive phenomenology, but this qualitative descriptive aims to explore issues including the recognition of sharing varied and interactive experiences that are inseparable from human interaction (Doody & Bailey 2016).

The sampling technique used by the researcher is purposive sampling, namely the determination of the sample by choosing according to the research objectives so that the sample

can provide the best information to researchers about the research problem being studied (Burchett 2014). Furthermore, the samples in this qualitative research will be referred to as participants. Therefore, it is necessary for participants who experience and understand the phenomena well related to research so that data richness and depth of information are obtained. The participants in this research were 14 participants because the data was already saturated. Data were obtained through in-depth interviews conducted for about 25–90 minutes during the interview, field notes were also conducted and recorded through a recorder after the participants signed the research informed consent.

Data analysis is used by using thematic analysis. Thematic analysis is a research method that aims to identify, analyze, and report patterns (themes) in data (Cooper et al. 2012). The first phase (familiarizing yourself with the data or data recognition). The researcher studied the data more deeply, by reading all the data repeatedly, the interview transcript at least 5 times, and listening to the audio recording at least two or more times until the researcher knew the most important content of the data. Then make notes in the form of a review by using the comment column on the computer or making highlights while reading, then print out a verbatim transcript and listen to the recording. Note comments or highlights followed by coding. The second phase (generating initial code). When the researcher reads the data and is familiar with the data, the initial research code or coding is produced. The code is done by identifying and labeling data that have potential or are relevant to the research question and are numbered according to the order that has been marked in the highlight. In the coding process, the researcher reads thoroughly each data item. After the researcher generates the first code. Then the researcher continued to read the data until he was able to identify the relevant citations for the next coding. The researcher repeated this coding process on all data items. The third phase (finding a theme). After all research data has been coded and all data has been identified. Then proceed with focusing on the data analysis process by pulling the codes into sub-themes. The researcher ends this phase by making a thematic map and compiling all relevant themes that have been generated in the thematic map. The fourth phase (reviewing potential themes). In this phase, the researcher refines the theme by checking the quality of the theme, such as considering the validity of each theme and the level of accuracy of the results. The next step is to read carefully and thoroughly and repeatedly the verbatim transcript that has been made in its entirety for each participant.

Ethical clearance is issued by the Ethics Committee, Faculty of Nursing, University of Indonesia (No. 63/UN2.F12.D/HKP.02.04/2019). This study uses the principle of research ethics Beneficence, in its application the process of collecting data the researcher tries to avoid questions that cause feelings of discomfort to the participants. During the study, the participants cooperated well and no interview process made the participants uncomfortable. Respecting human rights and dignity, the researcher first undertakes the obligation to provide a detailed explanation of the above to the technical interview process (time, place, and recording device). After that, the researcher gave the right to prospective participants to ask questions about other things that were not understood related to the research process and data collection. After that, the researcher gave the participants the freedom to decide to participate or refuse to participate in the study. The researcher prepared an informed consent form which became proof of the legal status of the participants in this study. The researcher does not force participants to participate in the research and/or compel other things that are not related to the research. Principles of Justice (Justice), in this study the rights of participants to get fair treatment and the right to maintain the privacy of participants. Nonmaleficence is a principle that means that any action taken to a person will not cause physical or mental harm (Aiken, 2004). During this research, explanations were given to all participants regarding the research process. In addition, the research explanation sheet was given to participants before the interview began so that if there were questions, they could be asked before the interview took place.

There are four criteria for data validity, according to Burchett, namely credibility, transferability, dependability, and confirmability (Burchett 2014). Credibility Researchers involve

participants in the data collection process, namely in choosing the time and place of the interview as well as the follow-up to the upcoming meeting to clarify information. Transferability, in this study, the researcher has made an explanation related to the research and explained it before the research process took place. Dependability is the role of other researchers acting as external reviewers in the entire process to report research results. Certainty (confirmability) is said to be objective if it gets agreement or approval from other parties on the views, opinions, and findings of research results, as well as the accuracy of the data. According to Polit & Beck, the accuracy of the data is represented by the information provided by the participants and the results of the appropriate data analysis, not directed according to the interests of certain parties (Polit & Beck 2014). This certainty is again proven by systematic examination by several people while still reflecting it with related journals. Systematic examination through decision-making on the choice of methodology, data collection, data analysis, and field notes used during the research process. This is to ensure the objectivity of a study so that there is no bias in the research results. This research has been carried out using reflection with related journals, choosing the right method and field notes, and analyzing the right data.

Participants in this study amounted to 14 people. 7 male participants and 7 female participants. The youngest participant was 21 years old and the oldest was 56 years old. The participants involved have a minimum experience of 1 time being deployed to a disaster area and a maximum of 4 times in the 2008–2018 period. The process of data collection and data analysis started on 11 February–8 April 2019.

3 THEMATIC ANALYTICS

This study uses a thematic analysis based on Clarke & Braun by identifying 2 themes related to the description of nurses' perceptions regarding the impact of natural disasters which will be discussed one by one regarding the identification of these themes (Clarke & Braun 2017). The themes identified in this study are 1) The negative impact of physical, psychological, and material losses after a natural disaster; 2) Positive psychological, social, lifestyle, and spiritual impacts after natural disasters.

3.1 *The negative impact of physical, psychological, and material losses after a natural disaster*

The first theme is the negative impact of post-natural disaster losses. There are 3 categories, namely physical trauma after a disaster, psychological trauma after a natural disaster, material damage after a natural disaster.

The first category is physical trauma after a natural disaster. This was expressed by P01, P05, P06, and P07 who said that there were people who were pinned against the wall, sleeping uncomfortably in the refugee camps and new problems arose in the refugee tents. In addition, new problems in the refugee camps have become one of the problems that refugees must face while being evacuated, such as ISPA, poor toilets, and mosquitoes. The presentation was started by the following participants:

“... there were some who complained that when they saw my mother come out and her feet were pinned by the wall, there were also those who suddenly saw that their house had collapsed and so on. Those are things that are often said by their victims, maybe because it was very deeply embedded in their minds when the earthquake occurred ...” (P01)

The second category is psychological trauma after a natural disaster. This was expressed by P01, P02, P06, P10, and P11 who said that the community still felt sad about this

condition, especially children, afraid of aftershocks and did not dare to return to their settlements. Participant quotes can be seen as follows:

“ ... Well if you look at the victim’s expression, it must be said, with a face that tells with a sad expression ... ” (P01)

“ ... At that time, it seemed that the children were afraid, they were afraid to be away from their parents ... ” (P02)

Natural disasters that occur create psychological trauma to the community, such as people who are afraid of permanent buildings, people affected by disasters feel that their cities are not safe and this disaster is an unexpected and shocking disaster for the community. This was conveyed by participants P07, P08, and P13. The explanation was stated by the participants in the quote below.

“...they don’t want to go back into the house because their shadow is that if they enter the house, their image is that they will experience an earthquake and the house will collapse, because indeed, the houses around there have been destroyed, so they are traumatized by the shape of the house. a building that is .. a permanent building ... ” (P07)

The impact of psychological trauma conveyed by participants P08, P10, P11, and P14 is that there are people who remain silent after the earthquake and they are still traumatized when the disaster strikes again. In addition, some people are still running when there is the sound of a truck passing near them, some are daydreaming and also confused about where they will go after the disaster ends. The presentation was started by the following participants:

“ ... they heard a truck pass by, they immediately ran away because of the trauma from the earthquake, even though only trucks passed ... ” (P08)

The third category is material damage after natural disasters. Material damage, one of which is damage to houses and residential buildings. This was expressed by P01, P03, P09, and P11 who said that there were people who lost their homes because their houses were destroyed, their houses collapsed and not all of the houses in the disaster area were damaged. Some houses have sunk to the ground and there are some that he is doing fine. Participants’ explanations can be seen in the following quote.

“ ... the next day someone will reveal material losses and some will lose their houses, so they will continue, well, eh, not to continue, for the future they have to think about how to live it in the future ... ”(P01)

Other material damage includes damage to infrastructure and other public facilities to reach the disaster area. This was expressed by P02, P03, P09, and P13 who said that there was cut-off road access to reach certain areas, water access was also difficult and facilities were limited due to natural disasters. This presentation can be seen in the quote below:

“ ... so the access is cut off, so what is striking is that the needs are lacking, including food, so on average water is hard to find... ”(P02)

“ ... in a disaster situation with limited facilities yesterday we (P03) ... ”

The impact of natural disasters can result in material damage, one of which is the death of the economy of the people who are directly affected by the disaster. This was expressed by participants P05 and P06 who said that people lost their jobs and income from tourist areas was lost due to the disaster. This is because the disaster struck in the tourist area so that the surrounding community lost their livelihoods and material income for their lives. Participants’ explanations can be seen in the quote below:

“ ... experienced loss of property, I think, their property, their house, their fields, their rice fields and then their income ... ” (P05)

In this study, participants revealed that natural disasters can harm losses after natural disasters. Post-natural disaster losses include personal injury and material damage, namely buildings and infrastructure as well as the economy. Trauma obtained after a natural disaster is physical trauma including injuries to body parts, experiencing hypertension compared to before being hit by a natural disaster, while psychological trauma includes anxiety, fear, sadness, and the loss of family members after a natural disaster. Meanwhile, other losses that occurred started from damage to buildings and infrastructure. The damage started from damage to houses, roads, public facilities such as hospitals and health centers. In addition, another loss is the disconnection of the wheels of the economy of the surrounding community which is directly affected by the mini-style disaster. The trauma that is still attached becomes a negative impact on people affected by natural disasters. Loss of both buildings and infrastructure is a natural thing to happen in disaster areas and a rehabilitation process is needed as soon as possible by the local government so that life can return to normal as before.

3.2 Positive psychological, social, lifestyle, and spiritual impacts after natural disasters

The second theme is about the positive biological, psychological, social, lifestyle and spiritual impacts after a natural disaster are formed from 5 categories, namely increasing self-potential, psychological improvement after a natural disaster, social improvement after a disaster, lifestyle improvement in life, and spiritual improvement.

The first category is increasing self-potential after natural disasters. This was revealed by P04, P07, and P12 that there was an increase in the potential of children to be enthusiastic about returning to school when there were people who survived the disaster who encouraged the victims who were directly affected and also the community was ready to help volunteers in every activity. The excerpts from the participants' presentations are as follows.

“ ... they are excited to go to school again ... ” (P04)

“...getting up doesn't take a long time, so there is a role for the community, related to mentoring in the community so that people wake up, not physically, yes, I mean infrastructure, so humans also need to be resurrected later, so they can continue to live in the future...” (P07)

The second category is psychological improvement after natural disasters. This was expressed by P05, P07 and P12 who said that the community was happy when they were allowed to return to their settlements to continue their life and appreciate the life given not to waste it after a natural disaster occurred. In addition, the community will not live in pride after a natural disaster occurs. The presentation was stated by the following participants:

“ ... the community must be able to get up and continue their life whatever happens, they must continue their life in the future ... ” (P07)

The third category is social improvement after natural disasters. Significant statements are expressed by P01 and P08. Participants said that many people live in one tent and eventually bring togetherness in that scope. In addition, there are activities that unite them so that togetherness remains between communities affected by natural disasters. Participants also said that there was an increase in solidarity between victims while in natural disaster areas. The quotations given by the participants are as follows.

“ ... yesterday no one rarely got together and so on and in this tent they gathered and so on because in the tent there were 5–6 families so the togetherness was increasing even though the togetherness was in a disaster situation ... ” (P01)

The category of social improvement after a natural disaster consists of several statements from participants regarding their concern for fellow survivors and the environment. This was expressed by P07 and P09 who said that the community cares more about the victim and other people are touched to help the victim and fellow victims are more concerned about one another. The presentation was stated by the following participants:

“ ... the earthquake knocked people’s hearts out to care for others regardless of religion, ethnicity, race, for example, not everyone would be touched by an earthquake to help like that, so the positive impact is externally, people are more concerned with people’s problems, right ... ” (P07)

Social improvement after natural disasters that occurred in the community was seen in good relations with other people while in refugee camps. This was expressed by P04, P06, P07, P13 and P14 who said that the community had begun to open up and help each other. In addition, the community is welcome with volunteers who help in the disaster area and support each other while in refugee camps. Participants’ statements can be seen in the quote below.

“ ... when I see that hope when they welcome people and volunteers, they start to cooperate, want to share their experiences and share their passion for life ... ” (P04)

The fourth category is the improvement of lifestyle in life after natural disasters. This was expressed by P01, P02, P04 and P12 who said that the community still has new enthusiasm and hope after a natural disaster and can think positively when a natural disaster occurs again. Participants also stated that in the future there will be a new life after this natural disaster that the community itself must go through. The presentation was stated by the following participants:

“ ... later there will be a new life that they will face according to what they just got from them after experiencing a disaster ... ” (P01)

The fifth category, namely increasing spirituality, was expressed by P04, P08, P13 and P14 which stated that people experienced an increased relationship with God. This increase in spirituality is not only in action, it will also enter the meaning of an event, especially in this natural disaster. Participants said that several people said that this disaster was a life lesson and people did not blame God but self-introspection. In addition, disasters are a reminder so that people can rise again and increase their faith in themselves. Participants’ presentations are as follows:

“ ... they didn’t use this disaster as a dead sentence that they had no future, instead this disaster was a lesson to learn how to live sincerely and give their best every second ... ” (P04)

In this study, participants revealed that natural disasters can cause positive psychological, social, lifestyle, and spiritual impacts after natural disasters. These positive changes start from increasing self-potential, increasing appreciation for life, good relationships with others, spiritual improvement in survivors, and concern for others and the environment. These changes occur in communities directly affected by natural disasters.

4 DISCUSSION

Based on the results of this study, there were 2 main themes, namely 1) The negative impact of physical, psychological, and material losses after a natural disaster and 2) Positive psychological, social, lifestyle, and spiritual impacts after a natural disaster.

The negative impact of physical, psychological, and material losses after a natural disaster.

The impact of natural disasters in addition to taking lives can cause infrastructure losses. These losses can affect individuals, families, communities, and the environment. These losses include material, physical and psychological losses (Al Khalaileh et al. 2012). These losses will be attached to individuals who experience trauma, one of which is a natural disaster. Inherent losses can be physical and psychological such as a physical injury due to exposure to building debris, deep sadness after being hit by a natural disaster, and can be trauma to the survivors in the disaster area (Meng et al. 2018; Polusny et al. 2008). The results of the research related to the theme of the negative impact of post-natural disaster losses show categories namely physical trauma, psychological trauma, and damage to buildings and infrastructure.

Physical trauma that occurs to victims varies depending on the type of natural disaster that occurs. Trauma such as broken bones, external injuries to external bleeding, or even internal organ bleeding can occur during an earthquake (Ramirez & Peek-Asa 2005). This is due to the ruins that occurred after the disaster directly hitting the victims. Physical trauma was conveyed by P01 who stated that there were people who were crushed by the rubble of their houses and external injuries that needed to be taken to the hospital for immediate treatment.

The adverse impact of disasters is not only physical trauma but also psychological trauma. Psychological trauma also appears in people who experience natural disasters. Psychological trauma can take the form of grief, loss of family members, and even PTSD after a natural disaster occurs (Meng et al. 2018; Polusny et al. 2008; Ramirez & Peek-Asa 2005). Based on the results of the study, all participants said that people affected by natural disasters experienced psychological trauma starting from the loss of family members, fear experienced by children, anxiety about the coming disaster again, and some participants said some victims did not move after the natural disaster occurred. . Based on participants P01, P03, P06, P07, P09, P10, P11, and P13 stated that one of the psychological traumas experienced by the community is that the survivors are still traumatized by the natural disaster. If the disaster happened again, especially during an earthquake, many people ran out of the tent and didn't think about the fact that it was still safe inside the tent.

Participants P01, P02, P04, P06, P07, and P09 stated that the psychological impact experienced by the community was more for the survivors who were still sad when the participants asked the survivors to retell related to the disaster that occurred at that time. The sadness that hit not only happened to parents but also happened to children based on participant P02. The sadness experienced by the children is that they are afraid of another disaster and also afraid of meeting new people, including volunteers in their refugee camps. This is in line with the research which states that children can experience PTSD after 6 weeks of the disaster (Dyregrov et al. 2018; Piyasil et al. 2007). In addition, children tend to express symptoms of depression in their daily lives after natural disasters hit them.

Physical and psychological impacts are the impacts experienced by individuals after natural disasters occur. In addition to these impacts, natural disasters cause material losses in the form of damage to buildings, the economy, and infrastructure (Fan et al. 2017; Mata-Lima et al. 2013). Damage to buildings such as damage to houses cut off-road access and many houses submerged during liquefaction disasters. Based on the results of the research participants with codes P01, P02, P03, P05, P07, P09, P11, and P14 which stated that on average 80% of the houses were damaged and destroyed to the ground. In addition, participants P05 and P06 stated that the community suffered property losses and lost income. Loss of income due to such as fields where work was affected by natural disasters and also villas where work was destroyed by floods. In addition, participants P02, P03, P09, P10, and P13 stated that the impact of this natural disaster damaged the environment, road infrastructure, and facilities so that access to the area was cut off. Participants P02 and P09 stated

that the impact of natural disasters damaged road access so that it could hinder the process of sending aid and also sending volunteers to disaster areas.

Positive psychological, social, lifestyle, and spiritual impacts after natural disasters.

The second theme in this research is the positive psychological, social, cultural, and spiritual impact of natural disasters which consists of 5 categories. These categories are 1) Self-potential enhancement; 2) Psychological improvement after natural disasters; 3) Social improvement after a disaster; 4) Improvement of lifestyle in life and 5) Improvement of spirituality. This category is an elaboration of the theme for positive post-disaster impacts. The positive impact is obtained from the process of someone experiencing a traumatic situation such as in a natural disaster. The positive impact can be in the form of self-resistance or resilience. Resilience is the ability that a person has to respond healthily and productively to a trauma. This makes a person have good coping in the face of subsequent trauma in his life (Adams & Boscarino 2006; Grotberg 2001).

Trauma that occurs can be in the form of a diagnosis of chronic disease, rape, disaster, accident, and other unpleasant experiences (Calhoun & Tedeschi 2014; Sigveland et al. 2012; Tedeschi & Calhoun 2004). The occurrence of trauma to a person can make a person experience the trauma so that if they get traumatized again they can develop good coping to deal with it. Self-defense can be influenced by experience, social support, and effective coping strategies (Brooks et al. 2020; Tausch et al. 2011). Based on research conducted by participants P04, P07, P08, P10, P12, P13, and P14, it was stated that people get an increase in their potential after a natural disaster. Specific to participants P04, P07, P12, and P13 stated that the survivors gave encouragement to other victims and could help volunteer activities while at the evacuation post.

One of the psychological impacts that occur on society is psychological improvement after natural disasters. This form of psychological improvement is that survivors can accept and apply the activities that have been taught to communities affected by natural disasters. This psychological improvement can be in the form of adaptive coping and positive hope when disaster strikes again. This is following the research which stated that hope and good coping can increase the adaptability of individuals who experience trauma (Ghiloni & Shaw 2013, Ho et al. 2013; Proffitt et al. 2007; Tausch et al. 2011). The results of the study found that participants P02, P05, P07, and P12 stated that the community had hoped to continue life after the disaster occurred and felt happy when they were told to return to resettlement.

The strength of this research is that it is carried out with qualitative methods and obtained appropriate interviews with participants who have been involved in handling natural disasters. In addition, researchers have deepened qualitative research before conducting this research by participating in training related to qualitative research. However, there are several weaknesses in this study, namely the limited interview process due to structured questions used by researchers to assist during the research data collection process.

5 CONCLUSION

This study aims to get a picture of nurses' perceptions related to the impact of natural disasters. The identified themes illustrate that nurses' perceptions related to the impact of natural disasters can have negative and positive impacts and require careful preparation from nurses before being sent to disaster areas. The description of the characteristics of the participants as many as 14 participants with gender 7 men and 7 women, besides the education of diploma III participants as many as 3 people, nurses as many as 6 people, masters 4 people and specialists 1 person. The ethnic variations in this study are quite diverse, namely from the Javanese as 5 people, Sundanese and Padang as many as 2 people, and Betawi, Palembang, Wakatobi, Dayak, and Bima each 1 person.

In this study, two themes were found that describe nurses' perceptions regarding the impact of natural disasters and were formed from 8 categories. The themes obtained are 1) The negative impact of physical, psychological, and material losses after a natural disaster, this first theme is a theme that was obtained from participants when participants saw the

conditions that occurred after a natural disaster. Negative impacts in the form of physical trauma, psychological trauma, and material damage must occur in every traumatic event for example in natural disasters, and 2) Positive psychological, social, lifestyle, and spiritual impacts after natural disasters, the second theme is formed from nurses' perceptions based on conditions that occur in the area the disaster. These positive changes start from changes related to themselves, changes in relationships with others, relationships with God, and changes in lifestyle after they experience a natural disaster. Recommendations for further research can dig deeper into the aspects of the impact of natural disasters on the survivors so that nurses can prepare themselves to be involved in post-disaster management.

ACKNOWLEDGMENTS

This research was funded through the PITTA B 2019 DRPM Grant scheme, University of Indonesia No: NKB-0492/UN2.E3.1/HKP.05.00/2019.

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Qualitative study utilization of complementary midwifery services on mother post partum

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ABSTRACT: Complementary obstetric services are one of the alternative options to reduce medical intervention in postpartum mothers. Complementary therapies that exist become one of the community treatment options, especially for postpartum mothers. Midwifery care is carried out by combining conventional and complementary obstetric services and has become an important part of midwifery practice. The implementation of complementary medicine in general has been regulated in the Decree of the Minister of Health No.1109 / Menkes / Per / IX / 2007 on complementary alternative medicine. The purpose of this study is to find out the use of complementary therapies in the care of postpartum mothers, the needs of complementary therapies of postpartum mothers as well as factors that influence the selection of complementary therapies in postpartum mothers and the reasons for using complementary obstetric therapy in Post Partum mothers. The research method used is a qualitative research method with phenomenological design. Data collection is done by way of an indept interview. The sample of this study was 6 postpartum mothers with purposive sampling techniques. As for the triangulation, the informant is 3 midwives who provide Post Partum services. Banjarnayar Research Place of Tegal Regency. Conclusion:, Postpartum has a good interest in using complementary obstetrics services in postpartum mothers, Utilization of complementary obstetric services in postpartum mothers, all respondents have used complementary obstetrics therapy, The need for complementary obstetrics services in postpartum mothers includes oxytocin massage, breast massage, postpartum massage, Factors That Affect the Use of Complementary Therapies During Post Partum is time, Midwives who are collective, friendly, distance and have baby children, The reason for choosing complementary midwifery services in postpartum mothers is by doing massages, touching the mother postpartum, providing comfort to postpartum mothers and reducing medical intervention.

1 INTRODUCTION

Midwifery services are an integral part of the health care system provided by registered midwives, can be done independently, with collaboration and referral. Midwives provide holistic midwifery care, humanistic based on evidence-based on an obstetric care management approach, and pays attention to physical, psychological, emotional, socio-cultural, spiritual, economic, and environmental aspects that can affect women's reproductive health, including promotive, preventive, curative and rehabilitative efforts in accordance with its authority in the Regulation of the Minister of Health No. 28 of 2017 on The Permit and Implementation of Midwifery Practices (Issel & Cook 1993, Kepmenkes 2007).

Complementary therapy is a therapy that is complementary and perfects conventional therapy, intending to complement conventional medical treatment, is rational and does not conflict with health law in Indonesia (Stöcker 2018). The implementation of complementary

therapy has been regulated in the Regulation of the Minister of Health of the Republic of Indonesia Number 1109 of 2007 concerning the implementation of alternative complementary medicine in health care facilities. Midwives can implement care for mothers and children by providing complementary services other than midwifery services according to applicable standards and regulations (Republik Indonesia Menteri Kesehatan 2007).

The use of alternative and complementary traditional health services in the world has become entrenched and has begun to be included in the individual health care system. Based on data from WHO, 80% of health practitioners in developing countries prefer alternative medicine to chemical medicine. Indonesia is a country rich in diversity of traditional medicine. The development of the use of traditional medicine has great potential for improving the health and welfare of the nation (Setyaningsih et al. 2020).

In Asia, The prevalence of CAM (Complementary and alternative medicine) use in postpartum mothers in the study population is high (85.5%). The prevalence of CAM use reported in a tertiary hospital in Malaysia is 87.3 and 83.2% in district health clinics in Malaysia. The reason postpartum mothers use CAM in Asia is that they are confident that CAM can help mothers restore strength, relax, minimize the risk of infection, restore body heat imbalance and facilitate uterine recovery after childbirth. In addition, most CAM users think that CAM is safe to use, easily available and cheap (Amirah et al. 2019; Nik Yusof Fuad et al. 2020). Indonesians who use alternative complementary medicine from doctors/health workers only 2.7%, the results of a survey in Indonesia that the use of complementary medicine is the highest based on reasons to try to maintain health. Traditional services are still obtained from not from health workers (Setyaningsih et al. 2020).

The postpartum period is important, because the risk of maternal and infant morbidity and mortality increases at this time. Bleeding is the main cause of maternal death in the world and mostly occurs before 24 hours postpartum. Therefore, birth attendants must ensure that the uterus is contracted properly, so that bleeding does not occur. The postpartum period is influenced by many factors, one of which is socio-cultural. Indonesia is a country that has socio-cultural diversity and has a tradition of maintaining health, especially for postpartum mothers. Management of services for postpartum mothers, apart from evidence-based obstetrics, sometimes postpartum mothers also use complementary therapies to deal with complaints experienced by mothers. Such as increasing the production of breast milk or reducing pain in the perineum wound. Apart from that, there are also several methods to speed up the recovery of the health condition of the postpartum mother (Widaryanti 2020). This study was conducted to know the use of complementary therapies in the care of postpartum mothers, the needs of complementary therapies of postpartum mothers as well as factors that affect the selection of complementary therapies in postpartum mothers, and the reasons for using complementary obstetric therapy in post partum mothers (Setyaningsih et al. 2020; Smith et al. 2022).

2 METHODS

The research method used is a qualitative research method with phenomenological design, to obtain the depth of data through the collection of deep data from respondents to find out how to use complementary midwifery in postpartum mothers, to the interest of mothers in using complementary therapies, the need to use complementary therapies in postpartum mothers, types of complementary services in postpartum mothers. Respondents in the study were midwives and postpartum mothers. Research tools using interview guidelines, research informants were taken using purposive sampling techniques, the number of main informants was taken back using snowballing sampling techniques and obtained 6 main informants, namely postpartum mothers and 3 triangulation informants of Independent Practice in Banjarnayar Tegal Regency, The study was conducted in November 2021.

3 RESULTS AND DISCUSSION

3.1 *Maternal interest postpartum in complementary therapeutic use in the puerperium*

Based on interviews of six postpartum maternal interests in complementary obstetric care.

Very interested because Very helpful with complementary obstetric therapy. (IU 1)

Yes, I'm interested in accompanying, helping people give birth. (IU 2)

Interest and support, so as not to give a little medicine, which is natural. (IU 3)

Interested, reduced medication and very helpful (IU 4)

I'm very interested, I like it, there is also an experience that breast milk is not smooth, then the midwife gives a touch on the back, massages. (IU 5)

Yes, I'm really interested, Mrs. Midwife has already helped. (IU 6)

Postpartum mom says she's interested in using complementary therapies to improve maternal health and reduce complaints of discomfort after delivery, help the healing process, help launch breast milk. The results of interviews from the 6 respondents showed interest in using complementary midwifery therapy in Post Partum mothers. Knowledge is the result of knowing, and this occurs after people sense a certain object. Sensing occurs through the five human senses, namely: the senses of sight, hearing, smell, taste, and touch. Most of human knowledge is obtained through eyes and ears. Knowledge is a very important domain for the formation of one's actions. Behavior that is based on knowledge and awareness will be more lasting than behavior that is not based on knowledge (Kostania *et al.* 2015; Setyaningsih *et al.* 2020).

Complementary therapies that exist are one of the community's treatment options, especially for pregnant women and childbirth. In various health care places, not a few clients ask about complementary or alternative therapies to health workers such as midwives. This happens because the client wants to get a service that suits his choice so that if the desire is fulfilled it will have an impact on client satisfaction. This can be an opportunity for midwives to play a role in providing complementary therapy (Altika & Kasanah 2021).

According to the midwife's information, many mothers postpartum have visited the clinic asking for complementary therapy to postpartum mothers. This shows the interest of postpartum mothers and the impact of developing complementary midwifery services on postpartum maternal patient visits, according to the results of interviews as follows:

Thank God, there have been more visits, maybe because many are giving birth, yes, most of those who visit are mothers who still have their first child. (IT 1).

Quite an increase, new mothers who visit, some ask for therapy that does not use drugs, but in another way, I finally gave complementary midwifery care. (IT 2).

Is, Alhamdulillah postpartum mothers who use complementary midwifery, people are happy. (IT 3).

The development of complementary midwifery services in the field was able to increase the increase in patient visits. The development of integrated complementary midwifery currently has considerable opportunities for the development of midwifery services, especially in diversifying the services provided and meeting the community's need for quality and affordable health services (Wahidin 2020).

Midwifery services are an integral part of the health care system provided by registered midwives, can be done independently, collaborate and refer to pregnant women, mothers in labor, postpartum mothers, newborns, toddlers and children. Parity is the condition of the mother giving birth to more than one fetus. Postpartum mothers who have children for the first time are new so they do not have experience so they visit health facilities such as midwives. On the other hand, mothers who gave birth to more than one had the assumption that they had experienced so that they did not visit/ask questions to health facilities (Jumiatusun & Nani 2020).

3.2 Utilization of complementary midwifery services in post partum mothers

Based on the results of in-depth interviews, which have been conducted regarding the experience of mothers in using complementary therapies during Post Partum, from the interviews, it is known that the majority of mothers have received complementary therapy from midwives in Post Partum.

I have just had one child, I have no experience, I feel stressed, with the presence of a midwife who provides complementary midwifery therapy solutions, my breast milk becomes smooth and no longer hurts, my body feels good, I don't feel achy... thank you midwife, no need to go away drug. (IU 1).

No need to use the medicine, it really helps after giving birth, no need to use medicine, with massage and touch it helps the milk to run smoothly and comes out a lot, it doesn't get clogged anymore. (IU 2).

My experience is that 1 week after giving birth, I visited the midwife's clinic, there was a postpartum massage, the midwife said to improve blood flow and increase the comfort of the postpartum mother, it turned out that after the massage the taste was very good, and breast milk was smooth. (IU 3)

Never had breast milk not smooth. I was stressed, I wanted to give formula, went to the midwife's place to try it so that the milk flowed smoothly, Alhamdulillah, the milk came out smoothly (IU 4) I

really like the method that doesn't use drugs, because I'm breastfeeding, I've had a bad body experience, Breast milk doesn't come out smoothly, go to the midwife for a consultation (IU 5)

Go to the clinic, because breastfeeding doesn't work when the first child doesn't have experience, the midwife gives a solution, breast massage so that the milk flows smoothly. (IU 6)

Mothers postpartum who use complementary midwifery care during the postpartum period has several reasons. One of the reasons is the holistic philosophy of complementary therapy, namely the existence of inner harmony and touch/massage in complementary therapy. Another reason is that mothers postpartum want to be involved in decision-making in treatment and improving quality of life than before. The existence of side effects from conventional treatment that is received causes choosing complementary therapies. This is what makes the current paradigm of midwifery services has experienced a shift. Midwifery care is carried out by combining conventional and complementary midwifery services, and has become an important part of midwifery practice. Existing complementary therapy is one of the community's treatment options, especially formothers postpartum. In various health care places, not a few mothers postpartum ask about complementary or alternative therapies to health workers such as midwives. This happens because mothers Post partum want to get services according to their choice, so that if the wishes are fulfilled, it will have an impact on client satisfaction. This can be an opportunity for midwives to play a role in providing complementary therapy (Altika & Kasanah 2021).

In Malaysia, CAM used by postpartum mothers to reduce pain and postpartum blood loss by promoting wound healing and improving uterine recovery, along with increasing the production of breast milk. Further, studies have shown that, by using CAM, postpartum mothers' general well-being can be enhanced by reducing weight, relieving constipation and improving symptoms of insomnia (Amirah et al. 2019; Nik Yusof Fuad et al. 2020). According to a US national survey, 37% of pregnant women and 28% of postpartum women reported using T&CAM in the last 12 months (Kumar Mohanty et al. 2020). Reports on the prevalence of CAM use vary widely in both developed and developing countries but the average results found a high prevalence (84.7%) of CAM use which was one of the highest reported in the literature. This variation could be as a result of what belongs to the CAM umbrella, nature, cultural values, belief systems, religious foundations and practices of our society, as well as the cost and level of accessibility of conventional medicine (Onyapat et al. 2007).

In Indonesia no law specifically regulates the implementation of complementary midwifery services, but the implementation of complementary medicine in general has been regulated in the Decree of the Minister of Health No. 1109/Menkes/Per/IX/2007 concerning complementary-alternative medicine. For many midwives and women, complementary midwifery services are an option to reduce medical interventions during pregnancy and childbirth, and experience this has been quite helpful (Republik Indonesia Menteri Kesehatan 2007).

According to information from midwives, the types of complementary midwifery services for mothers *postpartum* that are often of interest are oxytocin massage, postpartum massage, and breast massage, this is based on the results of interviews as follows:

Oxytocin massage, breast massage, because often with little breast milk, it doesn't go smoothly, mothers who have just had children are stressed, because there is little milk. (IT 1).

Some ask for a postpartum massage, yes, oxytocin massage, yes breast massage. (IT 2)

There are those who want their stomachs to be not distended, they want to be slim again, they want to lose weight, oxytocin massage, massage for postpartum mothers, breasts, yes, related to the postpartum period. (IT 3)

Regulation has been implemented for complementary medicine and therapy. There exist various forms of complementary therapy. Mind and body interventions encompass various practices such as hypnotherapy, meditation, spiritual healing, prayer, and yoga. Alternative medicine service systems encompass a variety of modalities, such as acupuncture, acupressure, naturopathy, homeopathy, aromatherapy, and Ayurveda. Various manual healing methods encompass chiropractic, healing touch, tuina, shiatsu, osteopathy, and massage. Pharmacological and biological treatments encompass various modalities, such as herbal remedies and alternative therapies like *gurah*. The dietary and nutritional strategies employed for the purposes of prevention and treatment encompass the adoption of a macronutrient-based diet, as well as the incorporation of essential micronutrients. Other methods of diagnosis and treatment encompass ozone therapy and hyperbaric treatment. (Republik Indonesia Menteri Kesehatan 2007). In 1998, the World Health Organization Traditional Medicine Team issued the publication *Regulatory situation of Herbal Medicines*. The terms “complementary medicine” and “alternative medicine” Complementary/alternative medicine often refers to traditional medicine that is practised in a country but is not part of the country's own traditions *Legal Status of Traditional Medicine and Complementary/Alternative Medicine* (Issel & Cook 1993; *WHO_EDM_TRM_2001*; World Health Organization 2019).

Based on the regulation of the Minister of Health of the Republic of Indonesia regarding the types of complementary therapies that have been recognized in Indonesia mentioned above, actually every health worker has legal protection to be able to provide health services using complementary therapies in accordance with the scope of services based on their profession. In midwifery services, almost all of the above can be applied by midwives to mothers and children.

Types of complementary midwifery services in the *Post Partum period*:(Kostania *et al.* 2015):

- Oxytocin massage: Oxytocin massage is a spinal massage on the 5th–6th ribs to the scapula which will accelerate the work of the parasympathetic nerves stimulating the posterior pituitary to release oxytocin.
- Postpartum Massage: This massage is generally carried out by midwives in the first week to the second week after childbirth. The aim is to improve blood flow and increase the comfort of postpartum mothers,
- Breast Massage: Breast massage referred to in this study is breast massage during the puerperium, aiming to facilitate milk production.

3.3 Utilization of complementary midwifery services in mothers postpartum

Based on the results of in-depth interviews, regarding the need for complementary midwifery services during mothers *postpartum*.

I once used the complementary therapy of oxytocin massage. (IU 1)

I am happy with all complementary midwifery services during childbirth, as long as I do not use drugs. (IU 2)

I like massages, the body feels good, everyone is happy. (IU 3)

I like oxytocin massage, breast massage so that breast milk flows smoothly, I don't have to use drugs (IU 4)

I like to drink herbal medicine, massage after giving birth. (IU 5)

Happy, massage breast milk smoothly, massage crew, while you can treat more healthy, and not at risk with me and my child. (IU 6)

Complementary midwifery services in question are health services provided by registered midwives that can be performed independently for pregnant women, mothers in labor, postpartum mothers, newborns, infants and children, as well as women of reproductive age and the elderly (Kepmenkes 2007). By applying non-conventional treatment (alternative and traditional) these services aim to support the normal state of the client or as an alternative option in overcoming complications or complications (Altika & Kasanah 2021).

There are also complementary therapies that call it holistic medicine. This opinion is based on a form of therapy that affects the individual as a whole, namely an individual harmony to integrate the mind, body, and soul into a single function. The need for complementary therapy can be adjusted to the needs of the mother, and midwives as service providers can improve services by providing complementary therapies.

Based on the regulation of the Minister of Health of the Republic of Indonesia regarding the types of complementary therapies that have been recognized in Indonesia mentioned above, every health worker has legal protection to be able to provide health services using complementary therapies in accordance with the scope of services based on their profession. In midwifery services, almost all of the above can be applied by midwives to mothers and children (Kostania *et al.* 2015).

The results of Suryawati's research in 2007 in Jepara Regency included 60 postpartum mothers, showing 41.7% abstained from consuming meat and fish, 83.3% of respondents did body massage to restore body fitness, and almost all respondents drank herbal medicine (Suryawati 2007).

3.4 Factors affecting the use of complementary therapy during postpartum

Based on the results of in-depth interviews, regarding the Factors Affecting the Use of Complementary Therapy During *postpartum*.

A midwife whose communication is good, not rude. (IU 1)

The distance from the house is close so I can go to the midwife's place. (IU 2)

Those who wait for the baby, usually wait for their husband/family who can take care of the child (IU 3)

Distance, time because there are babies, the midwife is friendly. (IU 4)

Time, it's hard to have small children (IU 5)

Nothing, the midwife is friendly, nice, kind, so it can be arranged to go to the clinic. (IU6)

Factors that are considered in the use of complementary therapies during postpartum include time, communication, friendly behavior of midwives, proper distance, and having babies (Setyaningsih *et al.* 2020). Possessing advanced communication skills facilitated midwives' ability to adopt a woman-centered approach and to be. Participants described the breadth of skills such as listening, hearing, clarifying, talking, providing verbal encouragement, and the effective use of silence (Bradfield *et al.* 2019).

According to information from midwives, the obstacles faced in complementary midwifery services for postpartum mothers were a lack of socialization to the community, inadequate community outreach (as not all people knew about complementary midwifery care), limited knowledge and experience, and the presence of traditional birth attendants in the village. This is based on the results of the following interviews:

Maybe not all of the people know about it, maybe they don't have enough information, maybe there's socialization

too. (IT 1)

There is still a dukun here, so sometimes there are people who run to the shaman. (IT 2)

In this case, the midwife must have knowledge, experience, additional training to support it. (IT 3)

The provision of complementary midwifery services can be an added value for the practice of independent midwives. By providing innovative services and services that meet their expectations, it has improved the quality of health services.

Witch doctors are partners with midwives whose existence is still highly trusted by the community. The shaman approach uses a family approach and upholds local customs, making it easier for the community to trust. The provision of complementary therapy is still assumed to be the authority of the shaman, and for that, there is a need for socialization and health education to the community that the provision of complementary therapy is a complement to the provision of conventional medical therapy. There is a need for socialization and promotion efforts to the community about the benefits of using complementary and alternative therapies as a complement to the provision of medical services and empowering midwives as facilitators for the community to increase promotive and preventive efforts through complementary therapies (Altika & Kasanah 2021; Issel & Cook 1993).

Efforts to disseminate information and knowledge about complementary therapies to the community can be carried out by midwives and other health workers through activities that are already running in the community, such as Posyandu, PKK activities, social gatherings, and recitation. With the provision of correct and continuous information, it is hoped that there will be a paradigm shift regarding the provision of complementary therapy services by health workers.

3.5 *Reasons for choosing complementary midwifery services for postpartum mothers*

Based on the results of in-depth interviews, regarding the reasons for choosing complementary midwifery services for postpartum mothers.

It's delicious, there is a touch from the midwife, it's more comfortable, rather than using drugs, I don't like taking medicine either. (IU 1)

Very satisfied with the midwife's service with massages, very helpful, no need for medicine. (IU 2)

It's better to choose oxytocin massage to facilitate breast milk, it is safer, more comfortable, the body is not tired. (IU 3)

I am happy with the current service at the midwife, there is a technique to facilitate it, the village people like to get a massage. (IU 4)

The midwife is friendly, cheap, there are other ways not to take medicine, because I've also been taking herbal medicine during childbirth, which haven't had a massage technique. (IU 5)

Happy, excited, you are fresh, breastfeeding is smooth. (IU 6)

Health services today are not just doing treatment, but also touching or leading to other dimensions in the patient, including emotional, psychological, spiritual conditions, to other environmental factors. The community's need for health is currently complex, and the cost of health services is also getting higher; meanwhile, people's purchasing power is decreasing,

and in the end, people are looking for other alternatives to get health. The above phenomenon spurs health service providers, including midwifery services, to develop services that meet the needs of the community, which are of both quality and affordability (Wahidin 2020). Complementary midwifery services are an option to reduce medical intervention in the *postpartum period* (Arimurti et al. 2020).

Doing massage and touching the postpartum mother provides them a sense of comfort and reduces medical intervention. The massage culture for postpartum mothers is still mostly done by respondents or relief of fatigue after giving birth; however, the amount varies for each respondent. The massage is given to a woman who is an expert in helping childbirth and caring for women after giving birth. Although there is not much scientific evidence to support the use of complementary therapies, based on the experience of *providers* and *users*, complementary therapies are safe and can be used in mothers and children. Complementary medicines used in the provision of complementary therapy are natural medicines, namely taking materials from nature. The ingredients commonly used in complementary medicine in Indonesia have generally been studied and investigated for their effectiveness and safety (Kostania et al. 2015). Pregnancy and childbirth constitute a time of transition in women's lives. Many women turn to complementary and alternative medicines (CAM) during Pregnancy (Pallivalappila et al. 2013; Mitchell. 2016).

According to information from midwives, the reason midwives practice complementary midwifery services for postpartum mothers is patient demand, reducing the use of drugs during the puerperium, and adding value to midwives. This is based on the results of interviews as follows:

Sometimes there are patient requests, reduce the use of drugs during the puerperium, to be closer to the patient, provide touch/massage, the patient feels comfortable, introduces the patient to complementary health services during the puerperium. (IT 1)

So that we don't take medication, because we are breastfeeding, we provide natural conventional therapy, providing information to patients with complementary midwifery services. (IT 2)

An added value for my BPM, there are patients themselves who ask to be massaged, support traditional natural treatments, so that they attract people to visit. (IT 3)

There are several reasons for midwives to practice complementary midwifery services for postpartum mothers, including the provision of complementary midwifery services that can be an added value to the practice of independent midwives. By providing innovative services and services that meet their expectations, it has improved the quality of health services. Client satisfaction is part of quality health services. The principle of improving the quality of health services is to meet the client's needs, namely by fulfilling the services desired by the client. By fulfilling the client's request, there will be a process of improving the process, quantity, and quality of service (Wahidin 2020). Limitations of this study: the authors only examined the phenomenology of Utilization of Complementary Midwifery Services postpartum; it is expected that further research will add variables, ways of sampling, and other methods to further refine this research.

4 CONCLUSION

Postpartum mothers has a great interest in using complementary obstetrics services; all respondents have used complementary therapies obstetrics. The need for complementary midwifery services in post-partum mothers include oxytocin massage, breast massage, and postpartum massage. Factors affecting the use of complementary therapy during postpartum include time, midwives who are collective, friendly, and distant, and the availability of baby children. The reason for choosing complementary midwifery services for postpartum mothers is by doing massage, touching the postpartum mother, giving a sense of comfort to the postpartum mother, and reducing medical intervention.

ACKNOWLEDGMENTS

The authors thank Harapan Bersama Polytechnic for supporting this research. The authors also thank respondents in Tegal Regency who are willing to be respondents in this study.

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